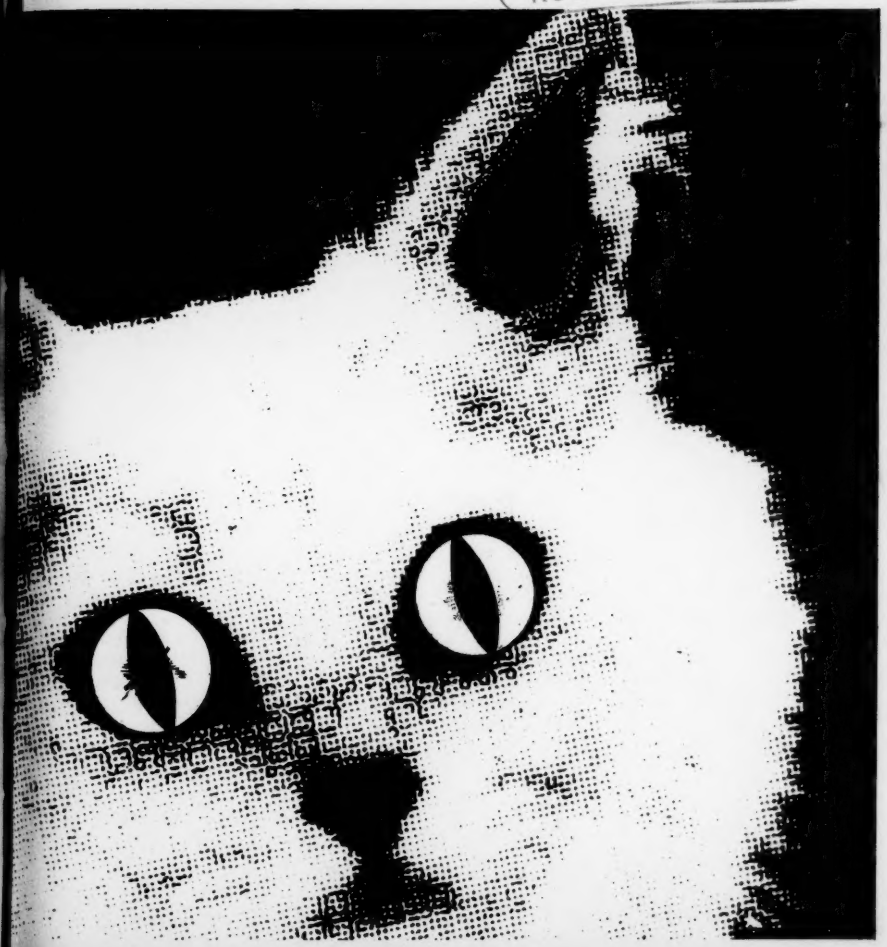
mental health digest

National Clearinghouse for Mental Health Information, Vol. 2, No. 9, September 1970

mhd

MAYO CLINIC
LIBRARY
SEP 21 1970
ROCHESTER, MINN.



cover story

This issue of the *Digest* contains a sampling of current research and discussions on a wide variety of problems concerning drugs. Why do drugs change behavior? Precisely what effects do they have on behavior? What are the physiological effects of drugs? Why do some people like to take drugs? These and many other questions must be answered through research with animals and human beings. Only then will there be a truly sound basis for the use of drugs in psychiatry, for the prevention of drug abuse, and for the treatment of drug dependence.

mental health digest

The *Mental Health Digest* is a monthly publication designed to reflect the whole spectrum of mental health and to present a broad sampling of scientific subject matter and professional points of view. It contains condensations of material selected from the current mental health literature. The condensations are published with the approval of the authors and publishers for use in the *Mental Health Digest* only.

Material contained in the *Digest* does not necessarily reflect the opinions, official policy, or position of the National Institute of Mental Health.

Editorial Advisory Board

Bertram S. Brown, M.D., Chairman

Robert A. Cohen, M.D., Ph.D.
John C. Eberhart, Ph.D.
Sherman N. Kieffer, M.D.
Gerald N. Kurtz
Eli A. Rubinstein, Ph.D.
Gian C. Salmoiraghi, M.D., Ph.D.
Phillip L. Sirotkin, Ph.D.
Nathan Sloate
Louis A. Wienckowski, Ph.D.

Editor: Lorraine Bouthilet, Ph.D.

The *Mental Health Digest* is available on subscription from the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402. Subscription price: $3.50 a year; Single copy: 30¢. For foreign mailing, add $1.00. (No additional postage is required for Canada, Mexico, and Central and South American countries except Argentina, Brazil, British and French Guiana, Surinam, and British Honduras.) Please make check or money order payable to the Superintendent of Documents. An annual subscription runs for 12 consecutive issues and begins with the next issue following receipt of the order. Back issues may be ordered at the single copy price. The expiration date is printed on the top line of the address label. Change of address and complaints about non-receipt of issues should be sent to the Superintendent of Documents, and should include the old address, preferably a mailing label, as well as the new address.

Use of funds for printing this publication approved by the Director of the Bureau of the Budget, May 20, 1968.

Behavior and Histopathological Findings During Chronic Methedrine Intoxication

E. H. Ellinwood, Jr. and O. Escalante

The amphetamine psychosis in humans develops over time with increasing doses. In a clinical study, an analysis of the behavioral sequences prior to and during the psychosis indicated that arousal mechanisms were being chronically stimulated at several levels in the central nervous system. From the behavioral observations, we concluded that there is a complex interaction being stimulated at several levels in the arousal systems. Observable behavioral components are noted in general arousal, focused attention, emotional arousal (fear), postural and cardiovascular changes, and changes in various stages of sleep. Systems with these observable components are successive levels of the reticular-activating system in the lower brain stem and mesencephalon, the midline and lateral nuclei of the thalamic activating system, extrapyramidal and limbic system, and cortical arousal areas.

Because neurophysiological studies demonstrated that the brain stem, specifically the mesencephalic reticular system was important for certain of the acute effects of amphetamine, it was decided to focus our studies of catecholamine depletion in the brain stem. Other areas will also be examined.

A total of 18 cats were observed under chronic or acute effects of methedrine (methamphetamine hydrochloride). The brains of five acutely intoxicated and five chronically intoxicated cats, along with a control for each, were examined for the distribution and intensity of monoamine fluorescence in neurons and nerve terminals.

Cats observed for acute effects of amphetamine were given doses of methedrine, 10–40 mg./kg. intramuscularly. Chronically intoxicated cats received two daily doses of methedrine intramuscularly at 8 a.m. and 4 p.m. for 14 days. Chronic cats were initially given 20 mg./kg. daily, and this was gradually increased to 50 mg./kg. daily. The behavior in acute intoxicated animals was observed for 2½ hours after the dose of methedrine. Chronic cats were observed for 2½ hours during the first acute dose, then examined periodically afterwards. Movies were taken of pertinent behavioral sequences, and the animals were sacrificed 3 hours after the last dose.

The brain stem, spinal cord, and some areas of the cortex in five cats on methedrine for 2 weeks were examined for catecholamine (CA), serotonin (5-HT) fluorescence (paraformaldehyde-induced), and acetylcholinesterase (AchE) activity. Untreated animals were used as paired controls.

Behavior with Acute Intoxication

One of the first observations that is noted in the acutely intoxicated cats is a loss of "normal" investigatory behavior. The animal stops moving into nooks and crannies along with cessation of sniffing and searching out smells. Even before the pupils begin to dilate, the cats become more attentive to objects in the distance. They are prone to react to small movements or sounds in the periphery. They gradually develop an increased mus-

Condensed with permission from *Biological Psychiatry*, 2(1):27–39, 1970.

cular tonus and this is associated with an increase in flexor reflexes. The cat stops moving, often develops an extensor wide base stance, primarily in the forelegs. Small twitches are noted about the face, especially about the eyelids. Although these cats "compulsively" attend to objects in the lateral distance, they disregard new objects put in their immediate vicinity even if these objects have movement, and will ignore a new cat placed into their immediate vicinity. Often they continuously look from side to side. Instead of visual searching, cats will maintain "compulsive" sniffing movements. They also appear to have quick righting responses. A few developed a fear and/or aggressive response which included crouching or hissing on approach; the emotional responses are noted after approximately an hour has elapsed, at which time they again begin to attend to objects in their vicinity. During a fearful period, they react to any approach reflexively with retraction of the lips and flattening of the ears.

Often the looking movements are sudden, as if the animal were responding to a stimulus in his lateral periphery. There are differences in responses dependent on whether the cat is stimulated by noises, movement, photography lights, handling by examining reflexes, or, whether it is left to sit quietly in the chamber. Stimulated animals tend to proceed into fearful stage much faster. Cats left alone may sit quietly and never exhibit the acutely excited phase. These cats are prone to develop repetitive, stereotyped patterns of looking or sniffing. In the beginning phases of stereotype behavior, it appears purposeful, but soon becomes repetitive. For example, one cat began sniffing the floor directly in front of him then suddenly turned to his right. The pattern evolved into a long sniffing sequence along the floor of the cage back to his feet, then suddenly looking to his right, followed by a quick turn toward his back. The pattern further evolved into sniffing which was followed by an abortive grooming of his right side, then turning to his right. This evolving sequence occurred over 600 times during a 2½-hour period. Another cat developed a similar pattern, and again it appeared to have its inception in purposeful behavior occurring just prior to onset of methedrine effects. The sequence began with sniffing the floor at his feet, then sniffing up the right wall of the chamber, pausing, then looking to the left. The sequence later evolved into looking to the right, then up and to the right, then turning quickly to the left. Both of these relatively sedate cats developed fear responses when they were taken out of the chamber. In animals that received a moderate degree of environmental stimulation, especially in the open during the observation period, the stereotype looking or searching from side to side gradually blends into fearful looking from one side to the other, searching then pacing, and in the more extreme cases, continuous circling. Animals left in their cages usually salivate profusely within 15 minutes of the injection; the latency of this response is prolonged when cats are in the open.

Changes in Behavior Associated with Chronic Intoxication

The changes noted with chronic intoxication are more variable. To a certain extent, the behavior depends on the predispositional behavior of the cat prior to intoxication; aggressive cats become much more aggressive. During the acute phase, the behavior described previously is noted. At ap-

proximately a week to a week and a half, the behavior begins to change markedly. This is associated with a decrease in tonus of the animal, and this is more marked in some animals. With the decrease in tonus, one begins to note postural changes. There is a decrease in the flexor reflexes, and there is an especial loss of tonus in the hind limbs. The cats lie down much of the time, especially during periods in which the last amphetamine dose was administered over 8 hours previously. They lie down and extend their hind legs, instead of the usual position with the legs drawn up under in a flexed position. At times they drag along with their front paws, letting their hind legs trail. The righting reflexes are markedly diminished. When given a dose of amphetamine, their response is of longer latency, and much less reactive. During this period the doses can be increased dramatically without major changes in behavior. Some cats have received up to 140 mg. a day. Often shortly after receiving the dose, these cats will regurgitate 3–5 cc. of stomach contents. They can, after amphetamine administration, have many of the same reactions of the acute cats, but this is much attenuated. During this period, these cats develop some fairly long-term behavior patterns, the most prominent being fear and aggressive behavior, or sterotyped behavior sequences. Some cats cringe in the corner of the cage, remain there, and are fearful of approach by the experimenter. They are extremely reactive to peripheral stimuli. Others are much more aggressive with hissing to almost any stimuli. At times, some of these cats appear to be reacting to stimuli that cannot be seen or heard by the examiner. Twitches of the face and eyes are common in chronic cats, as well as a tremor of the head, especiallly initially after the dose of amphetamine. One feature missing from all the cats was bruxism or a "compulsive" gnawing seen in rats and sometimes in amphetamine-intoxicated humans. Also missing, or markedly attenuated, were normal sniffing and investigatory behavior. The stereotype sniffing and searching became more repetitive in chronic cats.

Individual Variation

Although the amphetamine-induced patterns of behavior were typical from cat to cat, individual variation was noted especially in intensity and in the chronic emotional responses (e.g., fear and aggression). One cat never demonstrated the signs of chronic intoxication; muscle tone, righting reflexes, and stretch reflexes were maintained. Yet, this cat developed chronic aggressive and fearful behavior. The catecholamines were minimally depleted. Thus, the general lack of catecholamine depletion correlates with the paucity of behavioral manifestations.

In another cat, the greatest depletion was in the pons, lower medulla oblongata, and upper cervical region, with milder changes in the midbrain and diencephalon. Behaviorally, this cat demonstrated the most marked hypotonia, and decrease in righting and stretch reflexes. Behavior depletion correlations in other cats were often difficult to assess. Another cat developed the most marked chronic aggressive and fearful behavior. Toward the end of the 2-week period, any approach within 2 feet of this cat triggered intense hissing, often with crouching or turning onto the side to attack. There was little if any habituation of the hissing response on repeated approach. Responses could be elicited as often as every 5–10 seconds. Although this cat had

marked neuronal depletion in and around the lateral portion of the central gray matter of the mesencephalon and in the hypothalamus, areas where rage can be stimulated electrically, there was also fairly marked depletion elsewhere, including the pons and medulla oblongata.

Behavior-Depletion Correlations

It appears that amphetamine has a central effect on certain groups of neurons. The more drastic catecholamine depletion was in the nerve terminals. Nerve terminal depletion was noted in both acute and chronic animals; however, with chronic amphetamine intoxication, depletion of the neurons themselves is noted. Nerve terminal depletion after acute doses is in keeping with the excitatory behavioral effects noted in acute cats. The increasing amphetamine doses in most chronic cats eventually surpasses the ability of the neurons to resynthesize catecholamines, which is likely the primary factor involved in the marked tolerance that develops. It also accounts for the decrease in righting reflexes and tonicity.

The areas of neuronal catecholamine depletion were of interest because of the behavioral correlation with the areas affected. The areas of primary depletion in large areas of the reticular activating system, the hypothalamus, the amygdala, and parts of the hippocampus, did correlate well with the behavioral manifestations.

The acute manifestation of amphetamine is an intense general arousal which would be consistent with stimulating these systems. Beginning with an orienting response, these animals then began to look from side to side, searching, or attending an "hallucinatory-like" stimuli. This behavior gradually blended into fear and aggressive responses as the animal became much more aroused. The animal at this point would fearfully turn to look to one side; later, continuous circling was at times noted. Many aspects of the behavior demonstrated are also found as a consequence of stimulating in the same systems in which catecholamine depletion was noted.

Another characteristic in the acutely intoxicated animals was the hyperactive response to peripheral and distant stimuli. These animals would often attend very acutely to a stimulus coming from outside the experimenting room, but would at the same time pay very little attention to a similar stimulus in the nearby environment. These behavioral findings again correlate with the visual focusing mechanisms of the mesencephalon being affected. Hypertonicity increased righting reflexes and stretch reflexes in the acutely intoxicated animals, and hypotonicity decreased righting reflexes and stretch reflexes in chronic intoxicated animals. This behavior would be consistent with amphetamine having a major effect on the reticulospinal system, as well as in the vestibular nuclei, and in the cervical spinal cord. The reticular system involved would be those units in the lower part of the brain stem, including the mesencephalon, pons, and medulla oblongata. Stimulation of the lateral portion of the reticular system in the brain stem produces extensor hypertonicity and increase in stretch reflexes. Depletion of the reticular system in and around the vestibular nuclei is also consistent with the difficulties in righting, as well as the hypotonicity found in the chronically intoxicated animals.

In addition to the depletion found in neurons of small and medium size in the reticular system, there is also depletion of larger neurons in and

around certain cranial nerve nuclei; fairly marked depletion in and around cranial nerve nuclei was noted in the motor part of the 5th, 6th, 7th, 8th, 10th, and 12th cranial nerves. The 6th cranial nerve sits in juxtaposition to the parvocellularis and gigantocellularis of the reticular system. Lateral eye movements are prominent in the acute stage of amphetamine intoxication. The facial twitches and lip retraction noted with intoxication would correlate with the changes around the 7th nerve. In most other animals, including the rat and monkey, there is noted to be marked increase in biting and chewing responses; in man, it is noted that bruxism is a common symptom of amphetamine intoxication. In the cat, we looked specifically for chewing motions and found very few. It was noted that if the perioral skin were stimulated, the animals turned quickly to bite; however, chewing motions were not observed. There was a fairly marked depletion in and around the motor part of the 5th nerve. Increased salivation was noted in all animals, and usually occurred within a half hour after the initial acute dose. Salivatory nuclei (superior and inferior) are located between the genu of the facial nerve and hypoglossal nucleus extending laterally and ventrally through the reticular formation to the exits of the 7th and 9th nerves. In the chronic animals retching and regurgitation were noted at approximately the same latency as salivation. As is known, amphetamines decrease appetite and increase blood pressure. Methedrine stimulation of the 9th and 10th nerve nuclei and associated reticular area would be compatible with these findings. We found little change in behavior associated with the tongue, except in certain stereotyped patterns of sniffing and licking.

We have presented the theory previously that systems involving attention, specifically unilateral attention, are stimulated by amphetamine. We conceive of this system as having its highest elaboration in the cortex, perhaps in the frontal eye fields and cingulate cortex, as well as in certain areas at the temporal-parietal junction. Electrical stimulation of these regions, as well as stimulation of the amygdala, produces a unilateral attending response, depending on the side that is stimulated. These attending systems have rich connections with the thalamus and hypothalamus, and the mesencephalic reticular system. Also included in the mesencephalic-attending system are the cranial nerves for eye movement, and the medial longitudinal fasciculus which coordinates vestibular impulses, the tonic neck reflexes, and the eye movements. We conceive of these systems as being important to the animal in the wild. It would be equally important for these animals to have emotional responses involving aggression and fear, closely allied with these unilateral attending systems. It is apparent that stimulation in this system produces first, an orienting response, then the more intense fear and aggressive responses. It is also apparent that catecholamines are closely associated with these arousal systems,

Amphetamine: Differentiation by *d* and *l* Isomers of Behavior Involving Brain Norepinephrine or Dopamine

KENNETH M. TAYLOR and SOLOMON H. SNYDER

Amphetamine produces several types of behavioral effects. It enhances locomotor activity, an action which may be a model for the central stimulant effects of amphetamine in man, and it provokes a compulsive gnawing syndrome. These actions are thought to involve dopamine or norepinephrine, or both. Some studies implicate the corpus striatum in mediating the compulsive gnawing syndrome. Although indirect evidence suggests that norepinephrine tracts are important in effecting the enhancement of locomotor activity by amphetamine, some workers have favored a preponderant role for dopamine in eliciting this behavior.

Brain dopamine and norepinephrine are stored in distinct neuronal tracts. The corpus striatum contains high concentrations of dopamine and low concentrations of norepinephrine, while in most other brain regions norepinephrine is the predominant catecholamine. In nonstriatal brain regions, *d*-amphetamine is 10 times as potent as *l*-amphetamine in inhibiting catecholamine uptake by synaptosomes (pinched off nerve endings), while in the corpus striatum the two isomers are equally active. This uptake system is thought to reflect reuptake of catecholamine released at synapses in the brain accounting for the inactivation of synaptically released amine. Drugs that inhibit catecholamine uptake should potentiate its synaptic actions so that *d*-amphetamine should be markedly more active than *l*-amphetamine at synapses of norepinephrine while the two isomers would be equal at synapses of dopamine. Behavior mediated by brain norepinephrine might be affected more by *d*-amphetamine than by *l*-amphetamine, whereas behavior mediated by dopamine should be affected similarly by the two isomers.

We used male Sprague-Dawley rats. For biochemical studies rats were given injections of *l*-[^{3}H]-norepinephrine into the left lateral ventricle. Rats were decapitated after 5 minutes; the brains were dissected into different regions, and the concentrations of tritiated and endogenous norepinephrine were determined in each region. The rats were injected subcutaneously with 10 mg. of *d*- or *l*-amphetamine per kg. of body weight 1 hour before the administration of [^{3}H] norepinephrine.

For behavioral studies, rats were given prior treatment with iproniazid injected intraperitoneally 16 hours before the administration of amphetamine; iproniazid inhibits monoamine oxidase and facilitates the production of compulsive gnawing behavior. Control animals were injected with 0.9 percent NaCl. Rats injected with iproniazid alone did not differ from controls in locomotor activity and showed no compulsive gnawing behavior.

In behavioral studies rats were kept in individual cages with a wire grid floor and equipped with a light source and a photocell connected to a digital counter. Activity was measured as the number of times that a rat crossed the beam of light during a 30-minute session. Photocell recordings were initiated 5 minutes after injection of amphetamine. Compulsive gnawing behavior was assessed every 30 minutes

Condensed with permission from *Science*, 168(No. 3938):1487–1489, 1970.

after drug treatment. For behavioral studies, groups of six rats received amphetamine at 15 dose concentrations from 0.1 to 20 mg./kg. Each group of rats received only one dose of amphetamine, and a total of 180 rats were used.

In the cerebellum, the hypothalamus, thalamus, and midbrain, and the brainstem, *d*-amphetamine caused a marked reduction in the accumulation of the [^{3}H]norepinephrine while *l*-amphetamine had no effect. Because rats were killed soon after injection of [^{3}H]norepinephrine, the effect of amphetamine on amine accumulation is probably related to inhibition of neuronal membrane uptake rather than to effects on granular retention or amine release. *d*-Amphetamine but not *l*-amphetamine lowered endogenous norepinephrine concentration in these areas. In the corpus striatum, both *d*- and *l*-amphetamine caused marked reductions in accumulation of [^{3}H]norepinephrine without affecting endogenous dopamine or norepinephrine concentrations. These findings confirm in vivo our findings in vitro that in nonstriatal synaptosomes *d*-amphetamine is a more potent inhibitor of catecholamine accumulation than is *l*-amphetamine. We also confirm that *d*- and *l*-amphetamine inhibit to the same degree the accumulation of catecholamines into striatal synaptosomes.

d-Amphetamine was 10 times as potent as *l*-amphetamine in enhancing locomotor activity. With increasing doses of amphetamine there was an enhancement of locomotor activity up to a dose of 1.5 mg. of *d*-amphetamine per kg. or a dose of 12 mg. of *l*-amphetamine per kg. After these doses of *d*- or *l*-amphetamine, equal peak locomotor activity was recorded. Further increases in dose resulted in decreased locomotor activity.

There have been many theories to explain the stimulant action of the amphetamines in the brain. Our results suggest that inhibition of norepinephrine uptake may be a major mechanism of action. We also found that *d*-amphetamine was much more potent than the *l*-isomer in lowering endogenous norepinephrine concentrations.

d-Amphetamine was about twice as potent as *l*-amphetamine in evoking the compulsive gnawing syndrome. The greater similarity of the two amphetamine isomers in eliciting gnawing than in stimulating locomotor activity suggests that gnawing behavior is related to an action of amphetamine on striatal dopamine neurons. If gnawing were determined by dopamine tracts, *d*- and *l*-amphetamine should have been equal in their effects. The difference in potency of these isomers indicates that norepinephrine neurons may participate in production of this behavior, possibly as a triggering mechanism.

Because there are a large number of norepinephrine-containing tracts in the brain, pharmacologic criteria cannot readily delineate which isomer is involved in eliciting a given behavior. There are only a few dopamine-containing tracts in the brainstem. Besides the nigrostriatal tract, which appears to be related to the gnawing behavior induced by amphetamine, other dopamine tracts arising in the brainstem have terminals in the olfactory tubercle and the nucleus accumbens. A dopaminergic tract originating in the arcuate nucleus of the hypothalamus and terminating in the median eminence has been implicated in regulating the synthesis and release of pituitary trophic hormones. Experiments with *d*- and *l*-amphetamine may help to elucidate the functions of these tracts.

Altered Free Associations: Some Cognitive Effects of DOET (2,5-dimethoxy-4-ethylamphetamine)

HERBERT WEINGARTNER, SOLOMON H. SNYDER, LOUIS A. FAILLACE, and HERBERT MARKLEY

DOET (2,5-dimethoxy-4-ethylamphetamine) has received considerable interest since it is the ethyl homologue of DOM. (DOM has been used by hippies as a psychedelic drug, and is referred to as STP). Both DOET and DOM are methoxylated amphetamine compounds related to mescaline and amphetamine. The chemical structure of DOET has been predicted to have hallucinogenic or psychotomimetic properties. It was assumed that chemically related psychotogens could, nevertheless, produce different behavioral effects. Furthermore, similar subjective behavioral effects could be produced by different physiological and behavioral pathways. For example, subjects might report changes in perception attributable to alterations in cognition or, independently, altered perception may relate to changes in fixation, eye movements, etc.

In this study, the behavioral effects of small doses of DOET in normal adult males were contrasted with that of *d*-amphetamine. Preliminary work with DOET suggested it was likely to produce cognitive rather than perceptual changes. Free association and free recall techniques were used to study the effect of DOET on cognition. These techniques had the advantage of being short, easily administered, varied in the constraints placed on subjects in terms of the task requirements, and they are also interrelated.

Little constraint is placed on subjects in free association tasks, but nevertheless subjects usually give responses of high commonality, when compared to association norms. These associations are readily reproducible. It was felt that an unstructured cognitive task such as free associations would be particularly sensitive to DOET effects. In addition to studying free associations and recall, physiological and gross behavioral data were collected.

Ten emotionally stable subjects who were unsophisticated with respect to psychoactive drugs were selected from a pool of male volunteers. Ages ranged from 21–35. A psychiatric interview, Minnesota Multiphasic Personality Inventory, and a Thematic Apperception Test were used to screen out subjects who had psychiatric disturbance. All subjects with a history of extensive marihuana use or other mental stimulants were excluded. Subjects who passed the psychiatric screening procedure were paid $200 for the 2 days in which they served as subjects. They were told that the primary interest was in following the metabolism of a new drug that might also alter behavior.

In choosing an appropriate design it was useful to run each subject as his own control in a double-blind study and to choose an active rather than an inactive placebo. Since DOET was expected to produce some subjective behavioral changes, it would have been impossible to maintain a double-blind study with an inactive placebo. *d*-Amphetamine sulfate, given orally, was used as the active placebo. After the subjects

Condensed with permission from *Behavioral Science*, 15(4):297–303, 1970.

were screened, arrangements were made to hospitalize them, first for 48 hours and 2 weeks later for 24 hours. Only one subject was hospitalized at any given time. On the subject's admission, a physical examination was made during the initial 24 hours of hospitalization, and they were familiarized with all the procedures that were to be used in the experiment on the following hospitalization day.

The following morning and the morning of hospitalization 2 weeks later, base-line behavioral measures were obtained. Each subject was then administered either 10 mg. of *d*-amphetamine sulfate or 1.5 mg./70 kg. of DOET, in the hydrochloride form. The experimenter collecting behavioral data was blind to which of the drugs the subjects received on any given day. Each subject received both drugs, 2 weeks apart, and the order of presentation was randomized.

Starting at the time of ingestion of the drug, or active placebo, and then every 2 hours, the subjects were given a brief structured psychiatric interview which was tape recorded (the interview focused on subjective behavioral changes), administered some gross behavioral checklists, which included mood scales and a behavioral questionnaire sensitive to the effects of LSD-like drugs, measured for some physiological variables, including blood pressure and pulse rate, and given the cognitive procedures, which were the primary focus of this study. Urine and blood samples were also collected.

Free associations and their reproduction—Every 2 hours, the subjects were read equivalent lists of 25 words each, and were asked to say the first word which came to mind. The stimulus words within each list were controlled for occurrence frequency of the stimuli in English. The stimuli in each list were matched in terms of the pattern of free associated responses normally given to these words. For example, each list contained the same number of stimuli that produced a single very high-frequency associate and the same number of stimuli producing response distributions in which several words, rather than a single word, are frequently given in free association.

The experimenter recorded the subject's responses to each of the 25 stimuli on each trial. After the subjects had responded with a free association to each stimulus, the same stimuli were again read to the subjects in a different random sequence. The subjects were instructed to reproduce their previous associations and to guess if they were uncertain of their previous associated response. Reproductions of previous associations were recorded.

Free recall of random and organized words—On each trial, the subjects were read two different 40-word lists. One was made up of associatively related words while the other contained random words of the same frequency of occurrence in English. A 40-word list exceeds a subject's channel capacity; that is, subjects could not learn all the words on one trial. Each related word list was made up of two subgroups of 20 words each, which were generated from superordinate categories. These lists were designed by choosing the 20 most frequently occurring associations to each of two stimuli with the additional constraint that the words in each related set share no associations in common with the words in the other set used in the same 40-word list. For example, one list contained 20 words related to *vegetable* and 20 words related to *transportation*. Another list was made up of 20 words related

to *professions* and *animals*.

Word lists were read at the rate of one word every 2 seconds. The related word list was read in a random sequence; that is, associatively related words were not clustered together. Subjects were requested to try to remember as many words as they could, in any order. They recalled words orally with no time limit on recall.

Some Gross Behavioral Changes

With DOET most subjects reported mild euphoria, a pleasant experience, a slight difficulty in concentration, and increased talkativeness. No gross perceptual changes or behavioral effects were reported. DOET was reported to produce some mild visual effects in four of the subjects, which consisted only of closed-eyed imagery. No marked changes in pulse rate, blood pressure, or oral temperature occurred with either amphetamine or DOET. Eight did show some pupillary dilation with DOET.

Free Recall

Free recall of word lists was scored in terms of the number of words correctly recalled; the occurrence of intrusions (words recalled but not presented as stimuli); and an index of clustering, the tendency of subjects to recall related words in sequential runs rather than in a random sequence. As expected, the subjects recalled more related than random words and this was not altered by either DOET or amphetamine. Subjects did cluster related words on recall and the tendency to do so was not altered under DOET or amphetamine conditions. The only barely significant effect on free recall occurred with DOET at 4 hours after drug ingestion. This drug produced a small drop in the number of correctly recalled random words. The recall of related words was not affected by DOET. In general, it can be said that DOET (and amphetamine) did not alter free recall.

Free Associations and Their Reproduction

Responses given in free association were categorized as either high frequency responses, medium strength associates, low strength associates, and idiosyncratic responses. With respect to free associations, the subjects were a homogeneous group with no strikingly deviant subjects present. The screening procedure presumably helped achieve some of the homogeneity in the sample.

All subjects also demonstrated that their free associations were stable over time. All subjects reproduced at least 80 percent of their free associations.

The effects of DOET and amphetamine on the production and reproduction of free associations were examined at 2-hour intervals. Amphetamine produced no significant change in the proportion of high-frequency associations. However, DOET did produce a significant drop in the proportion of emitted high-frequency associations with a peak drop at 4 hours. The maximum effect of the drug on associative processes corresponded to the time of the maximal metabolic uptake.

The decrease in the production of high-frequency associations with DOET was related to an increase in the proportion of low and medium strength associations and not related to an increase in idiosyncratic associations. These associations were more unique, but were nevertheless appropriate responses to the presented stimuli.

The same subjects also gave fewer high-frequency associations 4 hours

after taking amphetamine although this finding did not reach statistical significance. The decrease in high-frequency associations with amphetamine was related to an increase in idiosyncratic responses rather than an increase in the more appropriate medium-low frequency associations.

Associations were at least as reproducible under DOET conditions as with amphetamine or the no-drug condition. In fact, DOET associations were somewhat more reproducible. The reproducibility data support the notion that the associations produced under DOET conditions are stable and tightly bound to the stimuli that elicit them, despite the greater uniqueness of these associations.

The determinants of the reproducibility of associations under DOET conditions were different from normal or amphetamine conditions. Normally high-frequency responses are more reproducible than lower frequency responses, particularly idiosyncratic responses. This was the case at base-line and under amphetamine conditions. One simple rationale for this finding is that idiosyncratic responses are less tightly bound to the stimuli which elicit them and are therefore more difficult to recall. The reproduction of associations is like that of paired associates learning in which the previous strength of the S-R relationship predicts ease of paired associate learning.

Under DOET conditions, the relationship between occurrence frequency of associations to stimuli and their reproducibility does not hold. Not only are subjects able to reproduce almost all of their associations but they are also just as likely to reproduce low-frequency responses as more frequently occurring associations. DOET-induced low-frequency associations are as likely to be reproduced as high-frequency associations. In effect, these low-frequency responses appear to be as strong, and as tightly bound to the stimuli which elicit them, as high-frequency responses to similar stimuli.

The results suggest that DOET, in low doses, produces changes in the subject's unconstrained cognitive processes, such as free associations. When constraints are placed on the subjects' thinking such as in a recall task, then DOET does not produce an effect, despite the fact that these more structured tasks are in part dependent on the subjects' free associations.

Given an unstructured set, the subjects seem to be "freed up" with DOET and produce less popular but relevant free associations. They maintain control and are aware of cognitive changes since they readily reproduce their associations while on the drug. Some of these behavioral effects of low doses of DOET suggest its possible use as an adjunct to psychotherapy, particularly with somewhat rigid psychoneurotic patients.

Abuse of Amphetamine and Amphetamine-Like Drugs

W. R. Clement, L. P. Solursh, and Walter Van Ast

The purpose of this paper is to review the status of abuse of amphetamine-type compounds and to comment on the street abuse situation in Toronto, Canada. In addition, it is hoped that by bringing the attention of responsible disciplines to the need for greater awareness of the probabilities and dangers of amphetamine abuse, there will be greater attentiveness to these problems.

Amphetamine is a mobile liquid with an amine odor and acrid burning taste. It volitalizes slowly at room temperature, is slightly soluble in water, and is soluble in alcohol, ether, and acids. An aqueous solution is alkaline to litmus and the minimum lethal dose orally in rats is 5 mg./kg. It is commonly available as the sulphate in *dl*- or *d*- form.

d-Desoxyephedrine HCl appears to be the most common amphetamine form in street use. It is crystalline, bitter to taste, soluble in water, alcohol, and chloroform. It is insoluble in ether. A 1 percent aqueous solution is neutral or slightly alkaline to litmus.

Low Dose Use: Pharmacology, Side Effects, Rationale

Amphetamine and its congeners comprise the basic ingredient of "diet pills." Dispensed by the billion, produced by the ton, these substances are to the public and much of the medical profession, a panacea for obesity, fatigue, and depression. They were first investigated in 1887, culminating in the synthesis of amphetamine in 1927 and of methamphetamine in 1929. These substances all have a basic phenylethylamine structure. This structure is basic also to adrenalin and explains the similarity of their pharmacologic action. Adrenalin (epinephrine), released particularly at time of "fight or flight," prepares the body for maximal physical output and mental alertness through its stimulation of the sympathetic nervous system (postganglionic adrenergic endings) and the central nervous system. The stimulant effect of all the amphetamines is similar, i.e., both peripheral (sympathomimetic) and cephalotrophic (CNS stimulating). Changes in subsidiary structure can qualitatively alter and partially dissociate these properties.

Compared with adrenalin, the CNS effects of amphetamines are quantitatively much stronger. As adrenalin does, they produce arousal, wakefulness, lessening of fatigue, and a sense of increased energy and self-confidence. They also produce euphoria—hence, its apparently logical use in depression and lethargy, in overcoming the sedating effects of other medications, or in narcolepsy. The exact nature or site of the central stimulating effect has not been elucidated.

The peripheral action will have some effect on practically every physiologic parameter. In the normal preparation for "fight or flight" most people have experienced many of these effects at some time; the heart rate and blood pressure increase, the pupils become widely dilated, the mouth becomes dry, there is relaxation of the smooth muscle of the G.I. tract, and of the muscles of the urinary bladder and bronchioles. These peripheral effects of amphetamines were responsible for their use in hypotension, asthma, and nasal conges-

Condensed with permission from *Psychological Reports,* 26(2):343–354, 1970.

tion. This use led to the introduction of the amphetamine sulphate inhaler in 1932.

Any drug with such a wide variety of effects will have undesirable side effects even at recommended dosage levels. Instead of alertness, or wakefulness, the patient may complain of nervousness, insomnia, headache, irritability, and excessively increased motor activity. The peripheral adrenergic effects may cause blurred vision, excessively dilated pupils with photosensitivity, too rapid a heart rate, palpitations, cardiac arrhythmias, and hypertension. The patient often complains of a very dry mouth. Nausea and vomiting, diarrhea, or constipation may all occur. Difficulty in urinating may be due to interference with bladder sphincter control.

To some extent, these complications are responsible for the gradual decrease in therapeutic indications for the amphetamines. Safer drugs with fewer side effects are now available for most conditions. Now indicated in a few rare conditions (narcolepsy, some hyperactive brain-damaged children), the quantity of amphetamines still legally prescribed can be attributed to two factors: continued belief in the amphetamines as effective anorexiants and/or ignorance of their abuse potential.

An increasing body of opinion suggests that the contribution of amphetamines to the long-term treatment of obesity is small or nonexistent. Some doctors believe that anorexiants should be used only when patients have tried and subsequently failed to lose weight satisfactorily by dietary measures alone. Once dietary restriction has proved ineffective, the weight loss that can be achieved by taking an appetite suppressant is, in relation to the degree of overweight, relatively slight.

High Dose Amphetamine Abuse

Abuse of amphetamines began almost as soon as they were marketed. Prison inmates soon learned how to extract the cloth strips inside nasal decongestant inhalers, soak them in coffee, and obtain an "amphetamine high."

During World War II, 72 million "energy tablets" were supplied to service personnel in Great Britain. The German Armed Forces also used it for its "central stimulant action." Dumping of similar military supplies by the Japanese in 1945 led to widespread public abuse. Early warnings about the psychiatric complications went largely unheeded, but control methods have now been imposed in several countries. There has been a constantly increasing awareness of the dangers of amphetamines. Sweden has withdrawn amphetamines from the market and in 1968 recommended to the WHO that amphetamines be controlled under the UN single convention on Narcotic Drugs. The British government recently cut off methedrine supplies to all physicians, dentists, and chemists. Further, the Ministry notified hospitals there would be a period of 1 year's grace for them. It is noteworthy that this action occurred after consultation with the responsible professional and governmental bodies; it was agreed by all that the medical requirements were so small as to inhibit black-market trafficking from legal sources. Concern was expressed, however, that the problem was already irremedial and a consequence of closing of licit channels would be to open a clear way for underground manufacture. This, of course, leads to impurities and illicit drug marketing.

The Syndrome and Its Complications

High-dose I.V. amphetamine abuse occurs in cycles: periods of wakeful-

ness lasting 3 to 5 days (maintained through repeated injection) followed by 34 to 48 hours' sleep. The injection produces "flash," "rush," or abrupt awakening, often described as "an orgasm all over your body." Often beginning with 20 to 40 mg. per shot, clinical tolerance soon develops and increasingly higher doses are required to obtain a good "high." Since commercial amphetamine has a concentration of only 20 mg. per cubic centimeter, it soon becomes necessary to make and inject a thick syrupy solution of crystalline methamphetamine ("speed").

At first, activity is purposeful. There is marked loquaciousness, decreased ambivalence, a sense of cleverness and "crystal-clear thinking" and an "invigorating aggressiveness" during the early phases of the "amphetamine run." With time, activity becomes less organized. It may become compulsive, repetitive, and grossly disorganized. The initial relief from anxiety from what others feel or think may soon be replaced by suspiciousness and self-consciousness.

Injecting more "speed" when he feels himself "coming down," the user becomes more agitated and suspicious. There is marked overreaction to slight movements in peripheral vision with visual hallucinations, hallucinations of voices, and delusions of persecution or gross paranoid reaction. It appears that the development of tolerance is a basic physiologic mechanism in the genesis of a stimulant psychosis. The paranoid state is seldom experienced during oral use or during the first few months of I.V. use. Although this psychotomimetic action of amphetamines has been recognized since 1938, it has yet to be adequately investigated.

The "action phase" may be terminated by the psychotic reaction or because the patient becomes too exhausted. He may sleep for 24 to 48 hours. Upon awakening, he is ravenously hungry and extremely depressed. This depression is often so severe and intolerable that he starts another "speed binge," and the cycle is repeated. Other users, particularly neophytes, may terminate a run because of a marked anxiety reaction. The acute psychiatric problems with which the high-dose amphetamine user may present are: exhaustion reaction, withdrawal reaction (severe depression), acute anxiety reaction, psychotic reaction. Suicidal or homicidal tendencies may be present.

The WHO Committee on Amphetamine Dependence denied the presence of a "characteristic abstinence syndrome." Nevertheless, the marked alterations in sleep patterns after prolonged use, the ravenous appetite and severe depression may point to what is actually a physical withdrawal syndrome. The clinical impression of markedly increased tolerance has not yet been confirmed in laboratory animals. In any case, uncertainty about physical dependence does not detract from the physical, psychiatric, and social damage amphetamine addiction produces.

High-dose amphetamine abusers may experience any of the side effects associated with low-dose usage. With the higher dosage these phenomena can be more marked. Intense central and peripheral CV stimulation may cause marked palpitations, extrasystoles, other serious arrhythmias, circulatory collapse, cerebrovascular hemorrhage, convulsions, and syncope. We have occasionally noted cardiovascular shock in the withdrawal state.

Insoluble impurities when injected may cause lung granulomata. Severe muscle tremors and joint or muscle pains are toxic effects which may oc-

cur after several days' use. These are signals to terminate the run. "Overdosing" may occur, accompanied by severe chest pain (anginal?), followed in a few minutes by unconsciousness which lasts an hour or so.

The general state of malnutrition leads to abscesses, nonhealing ulcers, chronic chest infections, brittle fingernails, etc. Frank vitamin-deficiency syndromes may occur. Use of unsterile equipment leads to local sepsis, systemic infections, and viral hepatitis. In an examination of 219 street users in Toronto, 53 had significantly elevated SGPT and ICD levels.

How Well Prepared Are We to Cope With the Growing Problem of Amphetamine Abuse?

We undertook a brief survey of the preparedness of the medical profession in a major North American urban area, to treat the problems presented by chronic use of amphetamine compounds. Two government-supported poison control centers located in large hospitals were contacted by telephone and presented with the problem of a youthful, chronic amphetamine user, now using I.V. at 3 grams per diem and having muscle spasms and psychotic symptoms. One center advised "discontinue amphetamine." The other advised that there were "no clear-cut issues with long-term toxicity." In both cases, a physician gave the advice, and in neither case was he able to indicate any treatment considerations.

The drug adverse-reaction center of the medical division of the Food and Drug Directorate reported receiving no notification in their files of methamphetamine toxicity. This occurred in spite of our awareness of an average of 20 cases per day of chronic amphetamine abuse in Toronto's general hospitals or Ontario Hospital emergency departments, as well as many others in outpatient clinics. The experience by the patient of frequent rejection as "hippy, dope addict" by several general hospitals is not irrelevant.

We advocate stopping the drug, usually brief hospitalization with close supervision, the use of NH_4Cl and a minor tranquilizer (a major tranquilizer if no LSD or STP type of mixture has been used), an anticonvulsant in case barbiturate withdrawal accompanies amphetamine withdrawal, an anti-agitational compound with supportive psychotherapy during the withdrawal phase; and social assessment and manipulation, the offer of more intensive psychotherapy, supportive chemotherapy where indicated, e.g., antidepressants, and the support of social agencies in the community on a long-term followup basis. Chronic amphetamine abusers tend to turn up again and again and generally present major problems in management which frequently result in significant social and therapeutic rejection by the patient and treatment center staff.

Marihuana and Temporal Disintegration

FREDERICK T. MELGES, JARED R. TINKLENBERG, LEO E. HOLLISTER, and HAMP K. GILLESPIE

Clinical studies of temporal distortions and disorganized speech in acute schizophrenia, as well as pilot studies with tetrahydrocannabinol (THC), led us to be interested in temporal disintegration. Temporal disintegration means that the individual has difficulty in retaining, coordinating, and serially indexing those memories, perceptions, and expectations that are relevant to the goal he is pursuing.

Temporal disintegration was measured by a task—goal-directed serial alternation (GDSA)—which required that the subject hold in mind and coordinate information as well as mental operations relevant to pursuing a goal. After giving the subject a starting number between 106 and 114, we asked him to subtract 7, then add 1, 2, or 3, and repeat such alternate subtraction and addition until he reached a goal between 46 and 54 specified for each trial. We randomly varied the starting point and goal so that different cognitive adjustments were necessary. The subject recited his mental operations aloud and worked as rapidly and accurately as possible, without using written props. The performance score gives equal weighting to the time taken to perform the task and to the number of mistakes made. Higher scores indicate greater temporal disintegration.

We employed two other cognitive tasks. The "regular serial subtractions of sevens" required that the subject begin at a specified number around 100 which again was varied at random, and then subtract sevens serially until zero was passed. Each subtraction makes use of arithmetic operations filed in long-term memory. The score gives equal weighting to the time taken and the number of mistakes made. The tests of short-term memory, the "digit spans forward and backward," were measures of the number of digits that the subject could accurately reproduce in the same or reverse order of presentation. For these cognitive tasks, we measured the upper limit of the subject's capacity for each testing session.

Tetrahydrocannabinol was extracted from marihuana supplied by the Bureau of Narcotics and Dangerous Drugs. The oral doses, calibrated according to the content of $l(-)$–Δ^1–THC, were 20, 40, and 60 mg. of THC. We also used a placebo, composed of an extract of marihuana from which virtually all the cannabinoids had been removed. It retained the characteristic disagreeable taste of the active material. The 40- and 60-mg. doses are probably higher than those obtained when smoking marihuana in social settings. However, previous studies of equivalent oral doses of synthetic $l(-)$–Δ^1–THC suggest that the induced psychotomimetic effects are clinically similar to those associated with smoking potent marihuana. The oral route, at least at present, offers a more precise way of regulating dosage.

Using double-blind controls, we gave eight normal male students the three oral doses of marihuana extract or placebo in randomized order on 4 different test days separated by at least 1 week. Doses were ingested after at least an 8-hour fast. Subjects were tested before drug ingestion and then 1½, 3½, and 5½ hours after

Condensed with permission from *Science*, 168(No. 3935):1118–1120, 1970.

ingestion. The same psychiatrist tested the same subject in an isolated, somewhat austere room. Both psychiatrist and subject knew that THC was to be given, but they were unaware of the sequence of doses and placebo.

Increased doses of THC progressively impaired GDSA performance. There were significant differences between performances on the GDSA at different doses. The poorest performances took place 1½ hours after THC ingestion, but there was a significant interaction between dose and time of testing, an indication that higher doses prolonged temporal disintegration.

By contrast, performance on the "regular serial subtraction of sevens" was not significantly impaired. Sustained attention and long-term memory operations, which are required by the task, appear not to be affected by THC.

Short-term memory was impaired. Both forward and backward digit spans were significantly decreased by all doses, although there were no significant differences between doses. Also, for all doses, digit spans returned to near base line at 3½ hours. Thus, in contrast to the progressive and more prolonged GDSA difficulties, impairment of the digit spans was not augmented by higher doses. This suggests that factors other than short-term memory may be involved in temporal disintegration.

Analysis of mistakes made during GDSA showed that, with increasing doses, there were progressively more errors in the serial or "working" functions of immediate memory. Serial immediate memory errors include loss of place, failure to alternate between subtraction and addition, and blocking. Serial immediate memory requires the subject to keep track of inputs at the same time that he manipulates them. Difficulties appear to be involved in temporal disintegration, because during GDSA performance THC induced more serial immediate memory errors, as opposed to miscalculations, when subjects got nearer to their goals—that is, when they had to begin making adjustments to reach their goals exactly. In switching back and forth between their most recent operation and the goal, the subjects frequently lost track of where they were. To quote one subject, "I'd pick out a number now and then go ahead. Coming back, I'd forget which number I just did or what I was supposed to do next."

With increasing doses, there were progressively more errors in reaching the goal. Of particular relevance is the mistake of disregarding the goal, which occurred only under drug conditions. Subjects kept going right past the goal until they checked themselves when they realized they had not brought the goal into awareness at the right time.

This temporal incoordination of recent memories with intentions may account, in part, for the disorganization of speech patterns that occurs under marihuana intoxication. The construction of meaningful speech requires that words and phrases be hierarchically ordered in a goal-directed fashion. If there is a deficiency in immediate memory, the components of speech become poorly interconnected over time, and the person is apt to lose his train of thought. "Loose associations" emerge, since ideas are determined primarily by recent or current stimuli rather than by a more extended temporal context of what has already been said and what is intended. Lack of goal-directedness and loose associations were common in the speech patterns of our subjects when they were under the influence of THC.

A Study of Ex-Prisoner Female Narcotic Addicts in Hong Kong

L. K. Ding and L. Y. Chan

Narcotic addiction is one of the most serious social, economic, and medical problems in Hong Kong. Workers in the field estimate the number of addicts to be between 60,000 and 80,000. This means that one out of every 50 or 70 persons in Hong Kong is an addict. The majority of the Hong Kong addicts are addicted to the "hard" drugs—heroin or opium. More than 80 percent of the prison population in Hong Kong are addicts.

An addict consumes an average of H.K.$10.00 ($6.05 H.K. = $1.00 U.S.) worth of narcotic drugs per day. It is estimated that H.K.$250 million are spent by addicts every year, an amount which is nearly double the annual Government budget for the medical services for the city. Narcotics are within easy reach of every addict because of the large quantities that are smuggled in from South East Asia.

Female addicts constitute about 3 to 5 percent of the total addict population in Hong Kong. Until the Discharged Prisoners' Aid Society started a modest treatment center for female addicts in 1967, no organized work was being done for these addicts. The Society felt that there was a great need to set up a treatment and rehabilitation center for female addicts, who were taking drugs surreptitiously in prison, or who relapsed to narcotics abuse after discharge.

The center consists of an apartment in a private multistory building sufficient to accommodate 12 persons at a time. It was started as a pilot project to see if female narcotic addicts could be treated for 2 months in a drug-free environment, followed by intensive aftercare work, consisting mainly of social rehabilitation such as attempts at family reconciliation, job training, and employment.

All those admitted came of their own volition. They were interviewed by the case worker followed by a routine physical examination. Anyone was eligible for admission provided she was a discharged prisoner without infectious disease. Oral methadone therapy was used for the period of acute withdrawal lasting less than 2 weeks in general. The starting dose was never more than 20 mg. per day, and it was rapidly reduced and completely withdrawn by the end of 1 week to 10 days. This report is based on 109 discharged female prisoner addicts treated at the center in 1967–68.

Although the greatest number (85) became addicted between 21 years and 35 years, nine persons became addicted while they were below 20 years and two while they were only 13 years old. The small number of younger addicts does not reflect the true picture of addiction among teenagers, as it is known that few younger addicts volunteer for treatment, for the simple reason that they can support their habit by prostitution—something which is not easy for the older addicts.

The largest number who volunteered for treatment came from the group ranging between 31 and 50 years. The youngest was 15 years old, and oldest 63 years old when they

Condensed with permission from the *Bulletin on Narcotics*, 22(2):7–11, 1970.

volunteered for treatment.

These 109 addicts had been taking narcotics for an average of 12 years per person, spending a total of at least H.K.$6,000,000 during this period or nearly H.K.$60,000 per person. This is a conservative estimate based on the average consumption of only $10 of drugs per person per day.

The high rate of illiteracy (62) among these female addicts is in great contrast to a group of 446 male ex-prisoner addicts in which there were only 52 illiterates. This is not surprising because of the prejudice of Chinese parents against educating their daughters.

Of the 88 prostitutes in the sample, 57 were first addicted to narcotics before becoming prostitutes. Similarly the 10 narcotic pedlars and pickpockets were first addicted before becoming involved in criminal activities. Prostitution obviously affords the easiest means for female addicts to maintain their habit. One addict revealed that she had been a prostitute for 6 years. Her average number of customers was 25 a day with a maximum of 60. Each customer paid $5 from which $3 was deducted for the procurer and other expenses, leaving $2 for the woman. After spending $35 per day to buy narcotic drugs, there was not much left for her living expenses.

Only 21 claimed to have been married or widowed. Of those who claimed to be widowed at least half had been deserted by their husbands, because of their addiction. Of the 88 persons who were cohabiting with others, five began this relationship before they were 16 years old. At least 20 percent of their male partners were drug addicts.

In view of the large number of prostitutes in this group the large number of positive tests for venereal disease (48.8 percent) is not surprising. In another study of 294 male ex-prisoner addicts tested for venereal disease only 20.8 percent gave positive results. The public health hazard this group of female addicts presents is quite evident. In this group heroin was the only drug used. Inhalation was used by 49, intramuscular injection by 23, and intravenous injection by 37. A novice usually starts by "shooting the ack-ack" in which some heroin powder is placed at the end of a cigarette which is then held in the mouth pointing the cigarette skyward before it is lighted to prevent the loss of powder. The addict progresses to "chasing the dragon" or "playing the mouth-organ." In both methods the heroin powder is placed on a piece of tin foil cigarette wrapper, and is heated by means of a small flame from a taper made of toilet paper or newspaper. As the powder evaporates it rises as a stream of smoke in the shape of an imaginary sinewy "dragon" which is then "chased" by means of a round hollow tube made of paper held in the mouth. Holding the outside cover of a matchbox in the mouth to inhale the heroin smoke is "playing the mouth-organ." This latter method is more efficient as most of the smoke is inhaled with little loss. Here it is of interest to compare the much larger number of female addicts, 60, who used injections with only 7 male addicts out of 174 studied. The reason for this larger number of female addicts using injections is not clear.

The common offenses for which they were convicted included possession of dangerous drugs and in many cases soliciting for immoral purposes. Gaol terms vary from 1 week to a few years. It is common knowledge that some addicts continue to get their supply of drugs surreptitiously

while in prison. The prison records show the futility of imprisonment in coping with the problem of drug addiction.

Information regarding the initial cause or causes of addiction is difficult to obtain, for often addicts would give different reasons to different workers at different times. In general it can be said, for those in the younger age group, that they were often introduced to the drug by their boy friends, who were themselves drug addicts. These male partners often induced their girl friends to the habit so that they could make use of them to practice prostitution.

Young bar girls and dancing hostesses are most vulnerable. Young male addicts being charged in court for living on the earnings of prostitution is common in Hong Kong. Sometimes these male addicts have several prostitutes under their control.

The women in our sample who became addicted when middle-aged or older were often from well-to-do homes. They were wives, mistresses, or concubines of wealthy people, who used to serve opium as a method of entertaining their guests. These women, many from mainland China, changed from opium to heroin after they came to Hong Kong.

A small group became addicted because of painful diseases such as peptic ulcer. Another minor reason is fatigue arising out of long working hours in factories. One of the girls who became addicted at age 13 was in school at the time of initial addiction. She began by going to parties in the homes of schoolmates. They then moved to dance halls and then to lodging houses. From her earnings through prostitution she supported several boy friends who were also addicts. This is a typical story.

Twenty-seven women admitted for treatment failed to complete the 2 months' treatment; 20 left of their own will, because they could not withstand the discomfort of the withdrawal symptoms in spite of substitution therapy, or, they felt well enough to leave before the 2 months' period was up, and seven had to be discharged prematurely because of disruptive behavior.

Of those 58 who are known to have relapsed, 23 relapsed within the first month after discharge; 16 after 2 months; eight after 3 months; four after 4 months; three after 5 months and one each after 6, 7, 8, 11 and 15 months. It is surprising that 10 out of 78 remained abstinent when the background of their addiction and the short period of treatment are considered. Of these 10 who are still abstinent two have remained so for more than 2 years, two for over 18 months, two for over 12 months, and four for more than 6 months. Of these 10 persons, their ages ranged between 30 and 57 and the duration of addiction averaged 14 years with a minimum of 8 and maximum of 24 years. It is of interest to point out that seven who were former prostitutes now have respectable occupations: three work as maid-servants, and four have become housewives. A study of the characteristics of those who have relapsed as compared with the 10 persons who did not reveals no clue as to the reasons for success and failure.

Drugs and Reality in Captive Society: Some Observations on Chemical Adaptation

GEORGE D. SCOTT

Man, in his search for personal comfort, meaningfulness, and identification, has struggled to adapt himself to the changing patterns of life, and has had to develop devious techniques to change his own attitudes toward the threatening and hostile world around him. Captive man is totally unable to escape from his reality in prison and as a result has to depend upon other means of handling his problems. In his anxiety and frustration he may attempt to form a dependency upon chemicals and drugs to modify his mental outlook upon reality.

In pursuit of his chemical adaptation, he has a number of channels open to him. He seeks out the medical officer, appears on sick parade and recites the symptoms of anxiety in the hope that sedative drugs will be prescribed. If he accomplishes his goal, his problem is over as he can balance symptoms and improvement to maintain an authentic relationship with the medical department. However, he may be disappointed with the doctor's prescription, and may search out other inmates who are saving their "pills" so that he can barter for the medication he prefers.

He may approach an officer to bring him drugs, or a drug cache may be arranged. He may even resort to alcohol. Crude alcohol has been produced in prisons in unusual ways.

Drugs which have reality-changing effects or comparable toxic effects are always in demand in prisons as the inmate seeks release from his anxieties. His frequent appearance on sick parade may be justified but he actually is trying to find a chemical solution to his problems.

An inmate who is not actually ill may develop complaints to obtain drugs which can be used as currency in the prison barter system, and he may pass them to a friend whose "needs" are greater than his. He may magnify his complaints with a view to "hoarding" medications against some future date when medication may be in short supply or when a parole turndown may make reality unacceptable.

Prisoners may use the sick parade as a social forum to establish communication with other segregated inmates. Complaints have to be presented to justify their presence, and the prescriptions are of secondary importance. Demand for drugs increases when a new medical officer appears because the inmates know they can take advantage of the medical officer who has prescribed only for his general practice. An inmate may seek his drug of choice with the argument that his "doctor in the street" prescribed it or another prison doctor ordered it for him.

Frequently requested are the amphetamines for narcolepsy, the barbiturates for some ill-defined epilepsy, and the maintenance tranquilizer used in another institution, either penal or mental. The rapidly reacting pentobarbitals together with the slower acting amytals are also requests of choice. Inmates desire a few moments of relaxation and will fight the soporific effects to enhance their

Condensed with permission from the *Canadian Psychiatric Association Journal*, 15(2):215–222, 1970.

mental ecstasy. These drugs have a high barter value and may even be used intravenously. Intravenous pentothal gives a prolonged period of relaxation and relief, and the motivation for a psychiatric catharsis has not infrequently sprung from the desire for a posttreatment jag.

Tranquilizers may form a habit relationship if given over a long period of time. Such tranquilizers as the phenothiazines and the fluphenazines have no exotic effects but sometimes place the inmate in a distant and removed state of indifference.

The meprobamates have potentially addicting properties in the dependent and in the alcohol addict, and the nonbarbiturate sedative has a useful role but inherent problems. A noncontrolled drug can be as dangerous as a controlled narcotic if used indiscreetly and routinely. Such medications include chloral hydrate, methylprylon and glutethimide, and other similar drugs.

Drug demands may be quite legitimate in situations of emotional stress. The inmate may be "shook-up" because of disturbing home news, prison difficulties, prerelease jitters, induction tensions, or may have a neurotic history indicating the need for some drug assistance. There may be some individuals who can only maintain their health in society and in prison through the use of tranquilizers and sedative drugs. Similarly, the symptoms of sleeplessness, irritability, and complaints of indigestion and tension may be checked out for authenticity with appropriate prescription for medication.

Medication in the prison setting should never be prescribed for prolonged periods of time. Liquid medication is preferred as it cannot be saved by storing in the mouth with simulated swallowing.

The use of cerebro stimulants must be carefully controlled as they produce a prolonged period of unreality, during which time the inmate may be involved in aggressive or violent behavior or promiscuity. The prison world is by nature depressing, and these drugs may temporarily medicate the inmate over a stress period, but in general are not particularly effective.

In women's penal institutions the drug situation is immeasurably complicated. If the woman offender has an addiction problem, imprisonment magnifies her tensions, aggravates her pathology, and pushes her frantically to chemical adaptation.

Women inmates function in various subcultural relationships. Ethnic groups are bound together, lesbian attachments are deep and establish barriers between inmate groups. Such love affairs may be stabilizing for brief periods of time but usually develop into highly possessive, demanding, and vindictive relationships.

Drug consumption in the female institutions demands frequent appraisal of the drugs being used and the inmates requesting help. Every inmate must be suspect of manipulation, saving, and merchandising her medications. A 1-month cutoff period every 3 months is a controlling device to reduce illicit supplies in the population, to remove pressure from the medical staff and in a devious way to inform the inmate that she cannot continuously satisfy her demands for chemical adaptation.

Chemicals and Poisons

In the prison geared to autonomy, training, and rehabilitation, chemicals form an indisputably important role. Chemistry plays an active part in our civilized culture, and these chemical relationships enter into a prison, wherein many normal activi-

ties must continue—preparation of food, servicing of motor vehicles, trades work in the plumbing, print, and tinsmithing shops, etc.

The average inmate is not cognizant of chemicals and chemistry, their combinations and effects. He hears anecdotes, listens to hearsay stories and may, in his desperate loneliness, search and find some chemical to solve his temporary anxiety. He may drink or inhale some chemical which he hopes will help him.

The chemicals involved with the alcohol formula, the methyl alcohols, the paraldehydes, the formaldehydes, other aldehyde compounds, together with solutions which have an alcohol evaporative quotient, are soon found to have an inhalant or ingestive quality. The effects of inhalant ether or ingestive chloral hydrate are soon determined. The inhalation of gasoline fumes from the garage, acetone from the paint shop, or of airplane glue from the wood shop are possibilities for the "trip-hungry" inmate. He may ingest liquids which smell like alcohol; typewriter cleaner fluid with its odd and deadly chemical effects may cause death through liver poisoning. Any chemical, unsupervised in the prison setting, may in a frantic moment be used by the inmate in his blind, impulsive, and unreasoning search for relief.

Mice pellets with a strychnine content can produce a period of mental excitement. Mild convulsive reactions occur in the course of their ingestion, and in large doses severe and fatal convulsions.

Mace and nutmeg have a yellowish volatile oil called myristica which produces excitement, delirium, and unconsciousness. Hepatic necrosis may be fatal. Taken in powdered form it produces a sensation of mental confusion and excitement, not unlike marihuana intoxication.

Women's cosmetics usually contain some methyl alcohol-type base. Stick cologne and stick deodorant may be melted down and taken orally. It has a disagreeable taste, is very toxic and results in visual blurring for a number of hours. Liquid perfume is mixed directly with a carbonated drink to produce a relatively short period of euphoria.

Cake shoe polish melted and strained may be mixed with orange juice to cause a few minutes of intoxication through the methyl alcohol effect.

Hair spray produces a dangerous and toxic effect. The liquid spray is mixed with hot water. It is very irritating to the throat, produces a period of mental confusion, indifference, with dizziness and blurring of vision. Residual toxic effects have been observed 2 weeks after ingestion with symptoms of cerebral irritability, increased sensitivity to noise, anger and visual complaints.

Nail polish remover can be used as an inhalant and has narcotic properties. If inhaled, it produces headache and dizziness—if ingested, drowsiness and confusion.

Turpentine cannot be considered palatable but it is used by the inmate by injecting quantities of the liquid into the muscles of the leg. A period of mental confusion and disorientation occurs. Usually the injected area sloughs out in a painful manner.

Industrial chemicals are extremely dangerous in the prison environment although they may be necessary in the function of the institution. Every chemical entering a prison should be registered. Its quantity, location, and qualities must be recorded in a toxic catalog so that its toxicology and antidotes can be made immediately available. Greater control must be exer-

cised by prison authorities to assure that no inmate can maim or destroy himself out of ignorance, nor should he be allowed to have access to chemicals which have reality-changing potentialities. There must be a daily rigid control over the chemical supply. Each shop supervisor should have knowledge of the toxic elements of chemicals used in his department.

Fermentation

The social captive, in his world of frustrations, searches for alcohol. It is to the captive a real product of days, weeks, months of thought, connivance and planning, and in prison must be catalyzed out of prison supplies. The essences are bread, breakfast foods, cereals and potatoes, combined with the fermentative qualities of yeast (and indeed of bread, not completely "raised"). Peculiar and comical situations have existed wherein the inmate has saved a bushel of breakfast food, dishful by dishful, but could not find the containers to "brew" it in.

The sophisticated inmate may be able to "work a brew," to sell for "civilian" dollars. Alcohol passes through the prison as air through a window, and the only evidence may be the changed behavior of the inmate. The fermentation periods center around times of inactivity, religious, or national holidays. The advent of the New Year produces a mysterious, mystical state wherein alcohol is the ritual spark.

Alcohol is not a real threat to prison life. Alcohol may make one man sleep, a second may become contemplative, and a third aggressive. In prison, behavioral qualities, not alcoholic qualities, form the baseline as it becomes a dangerous weapon when it excites man's mind to hostility, rebellion, and defiance.

The fermentation process has obvious complications. The smell of warm yeast, the dullness of carbon gas, and the symbiotic relationship of the peachfly to fermenting fruits, may give the telltale clues to "brew alcohol." One observant penal officer determined alcohol on his range by watching the "peachfly" population.

The medical officer must not allow himself to be identified as an inmate man or an institutional man. He cannot be party to any plan or activity either by the administration or the inmate population. He must function only in his role as doctor in the society of antagonists, and use his professional standards and his judgment to carry out his medical duties in his neutral position, to interpret the language of the two societies, and prevent both groups from using the medical department for reasons of their own.

The Experimental Use of Psychedelic (LSD) Psychotherapy

WALTER N. PAHNKE, ALBERT A. KURLAND, SANFORD UNGER, CHARLES SAVAGE, and STANISLAV GROF

The history of research with psychedelic drugs has produced a variety of methods for their use and conflicting claims about results. First came the wave of excitement in the 1950's when it was claimed that LSD could produce a model psychosis which might be useful in understanding schizophrenia. In the 1960's we saw attempts to test the efficacy and safety of psychedelic drugs for the treatment of various forms of mental illness, chiefly alcoholism. At the same time, there was a growing interest in these drugs by laymen for pleasure, excitement, mental exploration, and religious experience. The use of psychedelic drugs for all purposes has produced conflicting claims in the scientific and popular literature, intense public attention stimulated by the mass media, and legislative attempts at control of research and the black market.

Effects in Man Facilitated by Psychedelic Drugs

Psychedelic drugs are a special class of psychopharmacological agents, not to be confused with sedatives, stimulants, tranquilizers, anti-psychotic agents, or narcotic drugs. Psychedelic drugs are not physically addicting and produce different psychological experiences from these other drugs.

Five major kinds of potential psychedelic drug experience have been described:

First is the *psychotic experience* characterized by the intense, negative experience of fear to the point of panic paranoid delusions, toxic confusion, impairment of abstract reasoning, remorse, depression, and isolation or somatic discomfort or both.

Second is the *cognitive experience,* characterized by astonishingly lucid thought. Problems can be seen from a novel perspective, and the relationships of many levels can be seen all at once. The creative experience may have something in common with this kind of psychedelic experience.

Third is the *esthetic experience,* characterized by a change and intensification of all sensory modalities. Changes in sensations and perceptions occur: synesthesia in which sounds can be "seen," apparent pulsations of lifelike movements in objects such as flowers or stones, appearance of great beauty in ordinary things, release of powerful emotions through music, and eyes-closed visions of beautiful scenes, intricate geometric patterns, architectural forms, historical events, and almost anything imaginable.

Fourth is the *psychodynamic experience,* characterized by a dramatic emergence into consciousness of material that was unconscious or preconscious. Abreaction and catharsis may be experienced as an actual reliving of incidents from the past or a symbolic portrayal of important conflicts.

The fifth type has been called by various names: *psychedelic peak, cosmic, transcendental,* or *mystical,* and can be summarized under the following characteristics: sense of unity or oneness, transcendence of time and space, deeply felt positive mood (joy, peace, and love), sense of awesome-

Condensed with permission from the *Journal of the American Medical Association,* 212(11):1856–1863, 1970.

ness, reverence, and wonder, meaningfulness of psychological or philosophical insight or both, and ineffability (sense of difficulty in communicating the experience by verbal description).

Varieties of Psychedelic Drug Therapies

In experimental therapeutic work with psychedelic drugs, three approaches have evolved: psycholytic therapy, psychedelic-chemotherapy, and psychedelic-peak therapy. In evaluation of therapeutic effects, it is essential to keep in mind the differences in procedure, not only because different kinds of experiences are facilitated, but because conflicting results can be correlated with the method used.

In psycholytic therapy, which is practiced mainly in Europe, the aim is the uncovering of unconscious material which can be psychodynamically analyzed at the time and in subsequent psychotherapy sessions. This type is relatively long-term with multiple sessions over time and usually with small doses of the drug (25 μg to 150 μg).

In psychedelic-chemotherapy, the emphasis is on administration of the drug itself, during which limited psychotherapy may or may not be carried out. A single session with a relatively high dose of the drug (200 μg or more) has been the usual practice. This method is called hypnodelic when hypnotic induction is employed during the preparation for the session or before the onset of drug effects or both with the aim of providing better control.

In psychedelic-peak therapy, one distinctive characteristic and immediate goal is the achievement of a peak or transcendental experience, but just as important is the intensive psychotherapy which occurs in the weeks prior to the psychedelic drug session and the followup therapy in the weeks after to help with the work of integration. Preparation, which averages about 20 hours per patient, enables the therapist to establish close rapport with the patient and to gain intimate knowledge of the patient's developmental history, dynamics, defenses, and difficulties. In preparation for the session the patient is encouraged to trust the therapist, himself, and the situation, to let go of his usual ego controls and be carried by the experience, and to be open to whatever experiences he encounters.

The drug sessions are carried out in a treatment suite furnished as a comfortable living room. The patient's therapist and a psychiatric nurse are in constant attendance throughout (10 to 12 hours). For most of the session, the patient reclines on the sofa with eyeshades and stereophonic earphones, alternately listening to carefully selected classical music or interacting with his therapist. The function of the music is to help the patient let go, to enter more into his unfolding inner world of experience, and to facilitate the release of intense emotionality.

Although the LSD session is only part of psychedelic-peak therapy, it plays a unique and necessary role. In a dosage of 200 μg or more, LSD produces a 10- to 12-hour period of striking, varied, and anomalous mental functioning. Certain dimensions are therapeutically irrelevant (e.g., sensory changes) others have antitherapeutic consequences (e.g., panic, terror, or psychotic reactions). The major dimension with therapeutic relevance is the affective or emotional sphere; intense, labile, personally meaningful emotionality is produced with episodes of overwhelming feeling. The first several hours of a session are nonspecific

and pervasive; preoccupations and distress patterns are "broken" or fragmented, and recall for this period is poor. During the 3rd to 5th hours, psychedelic reactivity appears at peak intensity. The remainder of the session may be stabilized in an elevated mood state in which psychotic and other turbulent phenomena are no longer problems. Followup therapy begins during the reentry period of the session day and continues the next day as the patient and therapist review the events of the session and attempt to integrate them. The patient is encouraged to write a description of his experience.

If a psychedelic-peak experience has been achieved and stabilized, a picture which we have termed the psychedelic afterglow can be observed. Mood is elevated and energetic; there is freedom from concerns of the past and from guilt and anxiety, and the disposition and capacity to enter into close interpersonal relationships is enhanced. These feelings persist for from 2 weeks to a month and then fade into vivid memories that hopefully will influence attitude and behavior. During this postdrug period, there is opportunity for psychotherapeutic work on family or other interpersonal relationships.

Even with optimal programing, such peak experiences are neither universally achieved nor stabilized, and they do not automatically occur merely by administration of a psychedelic drug.

Research Projects With Psychedelic-Peak Psychotherapy

Since 1963, at the Spring Grove State Hospital, Baltimore, and continuing at the Maryland Psychiatric Research Center, research has been in progress to investigate the usefulness of psychedelic-peak psychotherapy with alcoholic, neurotic, and narcotic addict patients and patients who are dying of cancer.

Results are completed for a study of 135 alcoholic patients. The majority in both experimental and control group (117 patients) received one treatment with LSD. The 18 patients who had more than one LSD session were not different in psychological and social measures, but they received more average hours of treatment. Therefore, results were analyzed separately for the 117 patients who had only one LSD session (either a high or low dose). Of these patients, 104 were located for followup interview after 6 months.

In evaluating the findings in practical terms, we can say that a given alcoholic patient receiving a single high dose of LSD in the context of psychedelic-peak psychotherapy and experiencing a profound psychedelic-peak reaction has the best likelihood for improvement 6 months later. Within the context of our method, dosage appears to be a more certain outcome predictor than type of experience, although peak experiences do occur more frequently with high doses of LSD. Also, the estimation of psychedelic reactivity is probably not as reliable as the measurement of therapeutic outcome made by evaluators independent from the treatment team.

A project to investigate the effect of psychedelic-peak psychotherapy with narcotic addicts is underway, but it is too early for any indication of therapeutic outcome. These patients seem to have a greater degree of psychopathology than the alcoholics, but the skilled implementation of psychedelic psychotherapy seems to be proceeding smoothly. The character of the drug experience with LSD has been reported by the addicts to be

different from what they experienced under heroin (i.e., a confrontation with their problems rather than an escape from them).

We have been exploring the potential of psychedelic-peak psychotherapy with patients with cancer. The purpose has been to treat the depression, anxiety, psychological isolation, and intractable pain which so many of these patients face. The families, too, must cope with psychological problems. How to relate to the patient and what to tell him about his diagnosis complicates what is already a grim situation. This use of LSD is similar to that outlined, except that not quite as much time is spent in preparation, and the treatment takes place in a private room of a general medical facility. Also, family therapy plays a larger role.

We have treated 35 patients in a pilot project. Our findings must remain suggestive, but they do give some indications of the potential of this form of treatment. While not all patients were helped dramatically, none, even the most ill, appeared to have been harmed. This finding in regard to the safety of the procedure has been consistent with our results in alcoholic and neurotic patients.

The Question of Safety

When psychedelic drugs are administered under controlled medical conditions, permanent adverse effects have been rare. Many possible harmful physical effects have been suggested, but investigation has failed to furnish much conclusive evidence. Most recently, the question of chromosomal damage has been raised. Retrospective studies on persons having taken LSD (most from the black market and only a few under medical supervision) have produced conflicting reports.

Because we were in a position to study the effect of pure LSD of known amount on patients who were to be treated with psychedelic psychotherapy, we entered into collaboration with the cytogenetics laboratory at the National Institute of Arthritis and Metabolic Diseases to carry out a rigorously controlled study.

No difference was found in the rate of chromosomal aberrations before and after administration of LSD when the data from 37 individuals were analyzed. Also, chromosomal analysis was done on eight normal subjects who had received LSD in research experiments in the past, and no increase over normal chromosomal breakage rate was found.

Part of the conflicting evidence about the efficacy of psychedelic drugs as a therapeutic tool comes from the differences in the methods employed by various researchers. In spite of such diversity of approach, several points seem to be clear. Use of LSD is not a substitute for skilled psychotherapy. The evidence from the psycholytic use of LSD and psychedelic-peak therapy indicates that LSD can be an enhancer of skilled psychotherapy when integrated with an intensive psychotherapeutic program of sufficient duration (30 to 50 hours). The evidence concerning genetic hazards of LSD is conflicting and inconclusive. Much more research needs to be done in this complex area. Questions need to be answered, such as what kinds of patients will benefit most and under what circumstances. Newer psychedelic drugs may have advantages over more well-known ones.

Our research continues to intrigue us with the promise of psychedelic drugs, but they are powerful tools that need to be used and handled wisely.

Effect of LSD on Human Pregnancy

WILLIAM H. MCGLOTHLIN, ROBERT S. SPARKES, and DAVID O. ARNOLD

To evaluate the effects of LSD on pregnancies, we have studied the outcome of 148 human pregnancies following parental ingestion of this drug. The data are part of a larger followup study of 300 persons who initially received LSD orally in either experimental or psychotherapeutic settings during 1955 to 1961. Of this sample, 247 were located and interviewed in 1967 to 1968. The mean age of the sample of 247 at the time of LSD administration was 35 years; hence, only a minority (81) of the respondents (or their spouses) became pregnant subsequent to exposure of one or both parents. With the exception of induced abortions, the 148 pregnancies include all pregnancies which occurred in the sample between the time of initial LSD administration and the interview. Data related to pregnancies and LSD use were obtained for both parents; the remainder of the descriptive information is only for the parent interviewed (60 men and 21 women). All are white and typically of above average socioeconomic status. The mean age of the father and mother at the time of pregnancy was 34 and 30 years, respectively.

The number of medical LSD exposures prior to conception was small. For 47 percent of the pregnancies, it involved only a single administration for one parent. The range of combined exposures for both parents was 1 to 85, with 26 percent having 5 or more and 16 percent having 10 or more. The usual single dose ranged from 25 μg to 400 μg with a median of 125 μg; the maximum ranged from 75 μg to 500 μg with a median of 150 μg. The accumulated amount of LSD ingested prior to conception ranged from 75 μg to 10,000 μg with a median of 200 μg. For 27 of the 148 pregnancies, there was additional use of LSD under nonmedical conditions by one or both parents prior to conception. The range of medical plus nonmedical exposure for both parents was 2 to 165, with a median of 25. Information on the use of other drugs was available only for the parent who served as the respondent. For the 121 pregnancies where LSD exposure was restricted to medical conditions, the use of other psychotropic drugs prior to conception was minimal.

The spontaneous abortion rate for the group limited to medical LSD administration is 15 percent, which is within the usual range for recognized human pregnancies. The rate for those exposed to LSD nonmedically (37 percent) is considerably higher, although one woman in this group accounted for five of the 10 abortions reported. In this family, LSD was taken frequently by both parents before and during these five pregnancies, and one other abortion had occurred prior to the use of LSD by either parent (but subsequent to the use of peyote). A recent chromosome analysis (12 years after the first pregnancy) for the mother was normal; the father is deceased.

Both the groups receiving medically and nonmedically administered LSD reported more abortions when the mother (or mother and father) received LSD than when only the father received LSD. For those restricted to medically administered LSD, the percentage of abortions is 26 percent

Condensed with permission from the *Journal of the American Medical Association*, 212(9):1483–1487, 1970.

and 8 percent for maternal vs only paternal ingestion, respectively. For the combined medical and nonmedical sample, the corresponding percentages are 32 percent and 8 percent.

Of the 120 live births (67 boys and 53 girls), birth certificates were available for 81. The mean weight was 3,175 grams. Babies with birth weights of less than 2,410 grams were defined as premature; a gestation period of 37 weeks or less was used as the criterion when birth weights were unavailable. The percentage of live births that were premature is about the same as the norm of 7 percent.

Pregnancy outcome showed no direct relationship to the proximity of LSD exposure and the time of conception. The incidence of abortions and number of LSD sessions prior to conception showed a small positive relationship for the medical sample and a much stronger one for the group receiving the drug nonmedically. Of the 12 pregnancies when LSD was ingested during pregnancy, six ended in abortions, again, five in one respondent.

The one respondent in the group receiving LSD nonmedically who had had five abortions was already mentioned. Of the remaining 23 abortions, one woman accounted for three, and two other women had two abortions each. To eliminate any bias caused by including more than one observation per subject, the analysis was repeated, using only the first pregnancy which followed exposure to LSD. The abortion rate as a function of parent exposed to LSD for the 81 pregnancies in this category are essentially the same as those based on the full sample. For individuals restricted to LSD given medically, the percentage of abortions is 29 percent and 10 percent for maternal versus only paternal exposure, respectively. For the combined medical and nonmedical sample, the corresponding percentages are 33 percent and 11 percent. The results for premature births and proximity and number of LSD exposures for the sample of 81 are essentially the same as those for the full sample.

For each of the 120 live births, the respondent was questioned concerning birth defects and abnormal development in the child. There were 14 reported instances of "congenital anomalies," including minor anomalies not usually considered significant. In all 14 cases, LSD was limited to medical administration; the dose range was 75 μg to 250 μg.

The advantages of this study are: all of the persons in the study were exposed to pure LSD of a known dose; except for the small group who subsequently used LSD nonmedically, exposure to other drugs is probably not atypical; and there has been a relatively long-term followup. Limitations include: the doses of LSD used are generally low, and exposures were not frequent. While these results may not be generalized to persons exposed to frequent, large doses of LSD as well as other drugs, the following tentative conclusions may be made: there is no evidence that use of LSD *by men* prior to conception in the amounts described here is related to an increase in the rate of abortions, premature births, or birth defects; there is some indication that the use of LSD *by women* prior to conception may increase the incidence of spontaneous abortions, although the data do not permit the establishment of a clear-cut causal relationship; and there is little to suggest that exposure to LSD by either parent prior to conception and in the amounts described here increased the risk of having a child with a congenital defect.

Effects of Lithium Carbonate on Turnover and Metabolism of Norepinephrine in the Rat Brain—Correlation to Gross Behavioral Effects

K. GREENSPAN, M. S. ARONOFF, and D. F. BOGDANSKI

The effects of chronic administration of lithium carbonate on the turnover rate and metabolism of norepinephrine (NE) in brain was determined in an attempt to correlate these effects with plasma levels of Li^+. Pharmacological effects of Li^+ were also correlated to changes in NE metabolism. The doses of Li_2CO_3 and the steady-state plasma concentrations of Li^+ are similar to those found clinically in man.

Three groups of adult, male Sprague-Dawley rats were injected daily for 10 days with 1, 2, or 3 mEq./kg. Li_2CO_3, dissolved in 5 percent glucose. The dose of Li_2CO_3 was divided into two injections of one ml. each, intraperitoneally, 7 hours apart. Control animals were injected with 5 percent glucose.

On the 10th day the rats were anesthetized with ether and an opening in the skull was made. The next day, 46 ng. of *dl*–NE–7–H^3 in a volume of 20 μl was administered into the lateral ventricle of unanesthetized rats. At 2, 4, 8, and 10 hours, two animals from each group were decapitated, and the blood collected. The brains were removed, weighed (excluding the cerebellum), homogenized immediately in 0.4 N perchloric acid and assayed for H^3–NE and tritiated metabolites. Tritiated NE and its metabolic products were estimated by liquid scintillation counting. Li^+ and Na^+ in plasma were determined by atomic absorption.

Effects of chronic Li^+ treatment on plasma and brain electrolytes—The effects of Li^+ on the metabolism of brain NE were not caused by gross changes either in plasma [Na^+] or in total Na^+ or K^+ in the brains. The effects appear to be related to the presence of Li^+. After the 10th day, the steady-state [Li^+] in plasma was increased with increasing doses of Li_2CO_3 and [Li^+] in brain equaled that in the plasma of rats given 3 mEq. Li^+/kg.

Effect of Li^+ on the efflux of brain 11^3–NE, and on endogenous NE—The rate constant of efflux was increased from the control value of 0.0017 min^{-1} to 0.0044 min^{-1} by the 3 mEq./kg. dose of Li^+. These results suggest that the rate of NE turnover was more than twice the normal value. A smaller rate increase was produced by 2 mEq. of Li^+/kg; 1 mEq./kg. produced no increase.

Effect of lithium on the metabolism of H^3–NE in brain—Lithium$^+$ (3 mEq./kg.) increased the proportion of radioactivity in brain as deaminated O-methylated metabolites of H^3–NE at the expense of unchanged H^3–NE. The proportion of total radioactivity present as H^3–NE or H^3-deaminated O-methylated metabolites was not dependent upon time. The data for controls and experimental animals were pooled to obtain the mean for each. The pooled data showed that Li_2CO_3 reduced the proportion of total radioactivity present as H^3–NE from 58 to 50 percent and increased the proportion present as O-methylated deaminated metabolites from 38.4 to 45.1 percent.

Pharmacological effects of Li^+

Condensed with permission from *Pharmacology*, 3(3):129–136, 1970.

treatment—The daily administration of 3 mEq Li^+/kg. for 10 days produced death in 12 percent of the rats, usually after the 7th day, and an average weight loss of about 15 percent. Animals were sedated as indicated by their exploratory behavior, which lasted less than 1 minute as compared to 2 minutes in control animals. Rats given the smaller dosage were sedated for about 30 minutes after each dose.

A group of 10 rats were given 3 mEq. Li^+/kg. for 10 days and then given 70 mg./kg., intraperitoneally, pargyline on the 11th day. The animals became markedly hyperactive within 2–3 hours and showed increased sympathetic activity. Continuous fine tremors were also observed. Pargyline given to control animals did not elicit overt signs of hyperactivity within this time. A characteristic of Li^+-treated animals given pargyline was the prolonged duration of their exploratory behavior, lasting beyond 10 minutes, whereas animals given pargyline only explored up to 3 minutes.

Four hours after pargyline was injected, the concentration of NE in the brains of control rats and rats given 3 mEq./kg. Li_2CO_3 was 0.97 and 0.71 μg, respectively.

It is difficult to associate the sedative and excitatory effects of Li^+ with the increased turnover rate of NE. The increased turnover rate might be a response to the absence of negative feedback resulting from the increased metabolism of NE. After pargyline, the concentration of NE was lower in the brains of rats given Li^+ than in the brains of untreated rats, suggesting that Li^+ decreases the storage capacity of the brain.

Sedation might result from a deficiency of NE available to the receptors caused by the increased deamination of NE. Excitement in the presence of MAO inhibitor might result from the greater amounts of NE made available to receptors by the increased rate of NE synthesis resulting from the impaired ability of the brain to store NE. The findings suggest that the combination of Li^+ and MAO inhibitors in humans might have serious consequences.

These effects of Li^+ might affect behavior if they occurred at a small critical area of the brain, but there are other alternatives. We recognize another possibility in the light of the concept that synaptic transmission is mediated by newly synthesized NE. If the storage deficit caused by Li^+ affected the newly synthesized NE, this NE would be metabolized causing a deficiency in the amount of NE available to stimulate receptors and to maintain alert behavior. The deficiency of NE might explain the sedation that seems to accompany the decreased [H^3–NE] and the trend toward lower concentrations of endogenous NE. In the presence of pargyline, the newly synthesized NE would be protected and, therefore, available to stimulate receptors.

It is not established whether the changes in NE turnover or the alterations in behavior produced by [Li^+] in rats are related to the therapeutic effects of [Li^+] in mental disease. The important point is that these changes occur at plasma levels of [Li^+] that are not much higher than those attained clinically in the treatment of manic-depressive patients. It is of interest that more [Li^+] is retained in tissues of manic patients so that the overall tissue/plasma ratio of Li^+ is 1.4 compared to about 1 in normal subjects. Thus, a greater plasma [Li^+] in rats is required to produce tissue levels equivalent to those in manic patients.

Experimentally Induced Intoxication in Alcoholics: A Comparison Between Programed and Spontaneous Drinking

Nancy K. Mello and Jack H. Mendelson

One unanswered question concerning the behavioral and biological effects of alcohol on alcoholics is the extent to which correlates of drinking are a consequence of the pharmacologic properties of alcohol or of the pattern in which it is consumed. If ingestion of one quart of alcohol within a 24-hour period induced predictable and comparable effects, irrespective of the patterns of ingestion, then the behavioral efforts to simulate real-life drinking patterns would be unnecessary, and the application of programed dosage research paradigms to studies of alcoholism would be justified. If the pattern of administration of equivalent doses of alcohol does alter behavioral and biologic concomitants of drinking, then a reexamination of the significance of the usual research strategies for the study of alcoholism would be indicated.

Our studies of the effects of alcohol on biochemical and physiologic variables in the alcohol addict have used two basic paradigms: (1) a programed administration regimen in which alcohol is administered in divided doses once every 4 hours, and (2) some variant of free-choice administration in which the subject determines the periodicity and volume of his alcohol intake, constrained only by the total volume available over the drinking period. One advantage of the programed mode is that control of amount and time of administration makes it possible to construct time-dose-response curves. Free-choice administration does not yield dose-response relationships according to predetermined temporal intervals but does have the advantage of more closely simulating real-life drinking behavior.

We compared the effects of programed and free-choice alcohol administration in the *same* subjects over identical periods of time. Eight male volunteers from the alcoholic patient population at St. Elizabeths Hospital were subjects. They ranged in age from 37 to 45 and had a history of alcoholism of 12 to 27 years' duration. All were spree drinkers and six reported that cessation of drinking often resulted in withdrawal signs ranging from mild tremulousness to delirium tremens. All were in good health, and none had a history of neurologic disease; seizure disorder; hepatic, renal, pulmonary, cardiac or gastrointestinal disease; or nutritional or metabolic disorder.

Upon admission, the men were observed for 5 days, followed by a *programed* alcohol administration phase for 20 days. During this period, they were given bourbon every 4 hours around the clock. Dosage was gradually increased and during the first 3 days the daily doses were: 0.5 ml./kg. of 43 percent alcohol, 1.0 ml./kg. of 43 percent alcohol and 1.5 ml./kg. of 43 percent alcohol. This dosage resulted in approximate daily totals of 8 ounces, 16 ounces, and 24 ounces. Subjects were maintained for 14 days on the maximum dosage of 2.0 ml./kg. unless illness necessitated lower-

Condensed with permission from the *Journal of Pharmacology and Experimental Therapeutics*, 173(1):101–116, 1970.

ing the dosage. This dose resulted in daily totals ranging between 26 and 32 ounces. During the final 3 days, the dosage was reduced in 0.5 ml./kg. decrements to 1.5, 1.0 and 0.5 ml./kg. on consecutive days. A period of 10 nonalcohol days intervened before the free-choice drinking paradigm.

During the *free-choice* period, each subject was given 33 tokens each day which he could spend at any time during the 20-day alcohol phase. Each token purchased 1 ounce of alcohol. A possible alcohol intake of 33 ounces/day was selected to approximate the programed dosage maximum of the heaviest subject. There were no constraints as to how much alcohol a subject could buy at any one time. After 20 days, alcohol was no longer available, and subjects remained on the ward for a minimum of 10 days.

The following assessments were made: Prior to, during, and after each drinking period, blood alcohol levels were determined at 8 a.m., 4 p.m., and 12 midnight, with an instrument designed to measure the concentration of ethanol in the breath. Twenty-four-hour phenomenologic observations of sleep behavior were made on all subjects during the *free-choice* drinking period. These observations were subjective ratings by the nursing staff. They indicated whether a subject had been awake or asleep for most of the preceding hour, once each hour. A neurologic and mental status examination was completed daily on each subject by the attendant physician.

The following findings were obtained for all subjects: All drank more alcohol during the *free-choice* administration for at least 33 percent of the time available. These data are surprising since five subjects could not sustain ingestion of the programed maximum dose because of gastritis and vomiting.

All subjects, except one, showed day-to-day fluctuation in alcohol intake during the *free-choice* period. All subjects, except one, exceeded the intended free-choice daily maximum for some period of time.

During the *free-choice* period, all maintained blood alcohol levels that were 2 to 3 times as high as those measured during the programed period. When the daily volume consumed during *free-choice* was comparable to that consumed during the programed period, higher blood alcohol levels were observed.

During the *free-choice* period, subjects tended to consume more alcohol during a concentrated time even when daily totals were comparable. Consequently, they attained higher *peak* blood alcohol levels due to the difference in their pattern of drinking. The staff's assessments of inebriation during the two drinking periods were concordant with the blood alcohol level differences.

Tolerance—Some subjects maintained consistently low blood alcohol levels. One is of interest since he estimated his previous daily alcohol intake at 1 pint of whisky after work and denied experiencing withdrawal symptoms, but he was able to sustain a daily intake of 28 ounces of alcohol in divided doses for the 20-day period. Despite his relatively high consumption, he maintained low blood alcohol levels. Three subjects appeared to develop increasing metabolic tolerance throughout the programed drinking. During the final 7 days of maximal dosage, each showed a disproportionately low blood alcohol level despite sustained high intake.

Frequently, fluctuations in blood alcohol levels were unrelated to changes in volume of alcohol ingested.

It appears that these volume-independent variations in blood alcohol levels are related to the degree of metabolic tolerance and to the subject's food intake and/or gastrointestinal symptoms.

Blood alcohol level was rarely an adequate predictor of behavior. Clinical observations showed the expected correlation between inferred metabolic tolerance and degree of inebriation only during programed drinking. All subjects appeared more inebriated during free-choice drinking, even when the amount of alcohol ingested approximated that taken during programed drinking. Some subjects showed marked signs of disordered behavior with relatively low blood alcohol levels during both phases.

Withdrawal signs and symptoms—All subjects showed withdrawal symptoms. After free-choice drinking, all subjects showed more varied and persistent withdrawal symptoms than after programed drinking. The relative importance of interacting variables affecting withdrawal symptoms is difficult to specify. One factor is the greater volume of alcohol consumed during the *free-choice* period.

Abrupt cessation of drinking cannot account for the increases in withdrawal symptoms, since three subjects tapered drinking at the end of the free-choice phase and all reduced their alcohol intake at the end of the programed drinking period. Increasing or decreasing volume of alcohol consumed was not the sole determinant of blood alcohol levels. Even though one subject progressively decreased his alcohol intake at the end of the free-choice phase, his blood alcohol levels remained high. Another increased his intake during the last 5 days of the free-choice phase, but his blood alcohol levels remained low. It appears that insofar as withdrawal symptoms are related to the absolute level of blood alcohol levels and the rate of fall in blood alcohol levels, an alcoholic cannot manipulate either variable by his drinking behavior alone.

When considered as independent factors, neither volume ingested nor blood alcohol levels predict the severity and duration of withdrawal signs and symptoms. The crucial factor may be the rate of fall in blood alcohol levels considered in the context of the magnitude and variance of blood alcohol levels through time. This notion is consistent with the observation that many subjects exhibited *partial withdrawal* signs during the drinking period when blood alcohol levels were falling. A relative decrease rather than an absolute blood alcohol level also appears to be a significant determinant of partial withdrawal signs.

Sleep patterns—Upon initiation of drinking, the distribution of consecutive hours of sleep changed for all subjects. For three subjects most of the total sleeping time was distributed into shorter blocks of time relative to the predrinking baseline. The remainder showed an overall flattening of the distribution of consecutive hours of sleep. Two subjects slept in blocks of 1 hour and 10 hours with approximately equal frequency, and their sleeping pattern could be described as periodic alcohol-induced somnolence. The other three showed a fragmented sleep pattern insofar as more than half of their total sleep time was spent in blocks of time shorter than their normal sleep pattern. No subject slept significantly less during the drinking period. There was no consistent relation between fluctuation in volume of alcohol consumed and hours of sleep.

It is important to distinguish in-

somnia and fragmentation of sleep. The sporadic quality of sleeping characterizes an alcoholic's sleep pattern during inebriation. This distinction is important in analyzing sleep patterns during withdrawal. Only two subjects were initially insomniac relative to their baseline sleep pattern. Three of the five subjects showing the most prolonged and severe withdrawal signs slept about as long as during the predrinking base line. Four of the five subjects exhibiting the most severe withdrawal signs showed fragmentation of sleep patterns. These data suggest that fragmentation of sleep patterns is a reliable correlate of alcohol ingestion and a frequent accompaniment of alcohol withdrawal.

Physiologic and Behavioral Effects of Alcohol

What factors may have accounted for intersubject differences in blood alcohol levels observed during programed alcohol administration?

Adequacy of hepatic function—Although some subjects had low blood alcohol levels during the programed dosage study, not all showed evidence of metabolic tolerance. Although no subjects showed evidence of liver disease, the BSP and other liver function tests only provide an index of hepatic reserve. Subjects who did not show evidence of metabolic tolerance may have had some hepatic impairment which was not detected by clinical or laboratory methods.

Endocrine factors—Even if tolerance does occur in alcoholics who have adequate hepatic reserve and function, it is unlikely that this is a steady-state phenomenon. We observed marked fluctuations in blood alcohol levels which were not correlated with the volume of alcohol ingested. One factor which may be important is the magnitude of the adrenocortical response to ethanol ingestion.

What factors may have contributed to higher blood alcohol levels observed during the free-choice drinking? This phenomenon cannot be entirely explained by sampling factors since blood alcohol values were measured three times daily, and the final values are an average of these measures. The erratic pattern of food intake might explain the higher blood alcohol levels. In general, caloric intake from food sources other than alcohol was smaller during the free-choice study. Alcoholics may learn that eating less food enhances the intoxicating properties of a given dose of alcohol. If free-choice drinking is analogous to patterns of alcohol consumption which occur in real-life conditions, patterns of eating may also be concordant.

What factors may have accounted for differences in subject's capacity to tolerate alcohol between the programed and free-choice drinking paradigms? One possibility is that the sequential order of the two alcohol administration paradigms was paralleled by an alteration in some aspect of tolerance.

Tolerance—Since programed dosage was carried out prior to the free-choice experiment, some adaptive change in metabolic tolerance may have occurred as a consequence of the programed drinking. Metabolic tolerance may increase after chronic ethanol intake perhaps as a function of an adaptive increase in alcohol dehydrogenase or adaptive changes in hepatic microsomal enzyme systems. The duration of an alcohol-induced increase in metabolic tolerance is unknown but even if such a process were long lasting, it could not account for the differences observed in subject's

physiologic responsivity in these studies.

It is important to distinguish between metabolic and tissue tolerance. Alterations in metabolic tolerance would not explain the high incidence of gastrointestinal symptoms during programed administration. However, development of tissue tolerance could account for a decrease in gastrointestinal symptoms during free-choice drinking.

Pattern-related effects—An alternative explanation is that small, frequently administered doses of alcohol are more toxic than higher, more widely spaced doses. Examination of the possible significance of dose-periodicity may clarify the administration-specific effects of alcohol on behavioral and biologic processes.

Man can metabolize alcohol at a rate of about 1 ounce per hour. During programed administration, the amount of alcohol delivered every 4 hours produced peak blood alcohol levels which should have been significantly reduced before administration of the next dose. Subjects were exposed to six ascending and descending blood alcohol levels each day for 20 days; during free-choice drinking, subjects could sustain a blood alcohol level and avoid a series of abrupt changes.

An abrupt rate of change in blood alcohol levels during programed administration may have produced a variety of toxic effects. There are data which suggest that ascending blood alcohol levels have a different effect on behavioral and physiologic indices than descending blood alcohol levels. It is possible that a repeated challenge to systems responsive to ascending blood alcohol levels gradually exhausts their potential for an adaptive response.

Withdrawal Signs and Symptoms

The occurrence of withdrawal symptoms upon cessation of drinking is a major pharmacologic criteria of alcohol addiction. Some clarification of the determinants of withdrawal phenomenon are provided by our observations. These data testify to the importance of the pattern of drinking as opposed to duration of drinking as a critical determinant of withdrawal duration and severity. It is important to reemphasize that the mode alone cannot account for the differences in severity of withdrawal signs. This finding is not inconsistent with the notion that gradual reduction of alcohol intake may be effective in decreasing the incidence and severity of the alcohol withdrawal syndrome. However, the expression of partial withdrawal symptoms is difficult to predict on the basis of the magnitude of change in blood alcohol levels.

Since all subjects drank more alcohol during free-choice, it is difficult to isolate the contribution of the pattern of drinking and the overall volume ingested in precipitating the withdrawal syndromes. However, two subjects drank similar quantities of alcohol during the two periods, and both showed the most varied, severe, and prolonged withdrawal syndromes after free-choice drinking. This suggests that pattern of ingestion may be more significant than volume in accounting for the consequences of cessation of drinking. This impression is qualified by the fact that multiple determinants relate both pattern of drinking and volume ingested to blood alcohol levels measured.

The difference in withdrawal phenomenon after the two drinking patterns is not a function of the sequential drinking experience insofar as this might produce a general decrease in physical health or intercurrent ill-

ness. Most gastritis and intercurrent illness occurred during programed drinking, and all subjects were better able to tolerate drinking during spontaneous drinking. A history of alcohol withdrawal appears to be the best predictor of alcohol withdrawal phenomenon.

Alcoholics may experience withdrawal symptoms during a drinking episode if their blood alcohol level falls rapidly, even though this fall may be relatively small. Perpetuation of drinking by alcoholics may be, in part, an attempt to reduce symptoms associated with partial alcohol withdrawal. Such a notion would be consistent with a concept of physical dependence which attempts to ascribe motivation for drinking to a biologic or physiologic need.

Alcohol-Induced Disruption of Sleep Patterns

The observation of sleep fragmentation as a consequence of alcohol ingestion may be related to other behavioral and affective changes associated with sustained inebriation. Alcohol produces increases in anxiety and depression in the alcoholic, as contrasted to the nonalcoholic individual. The affective discomfort during chronic intoxication is similar to that reported by subjects deprived of Stage I rapid eye movement (REM) activity. It is not known whether alcohol-induced sleep fragmentation is associated with changes in overall Stage I REM activity.

The observation that sleep fragmentation may correlate with severe alcohol withdrawal signs and symptoms is contrary to most clinical reports of insomnia during withdrawal. Our data suggest that withdrawal symptoms may correlate with a disruption of sleep pattern but not necessarily with changes in total hours of sleep.

The pattern of drinking produces discernible differences in physiologic and behavioral correlates of intoxication and withdrawal. The magnitude of these differences suggests that the time-programed dosage research paradigm may give a different picture of the alcoholic's response to alcohol than a paradigm which allows spontaneous alcohol consumption. Results obtained with programed alcohol administration may be of more limited generality for understanding the biologic and behavioral aspects of alcoholism as expressed in real life.

Covert Reinforcement

Joseph R. Cautela

The term "reinforcement" as used here refers to any stimulus which increases the probability of a response when it is presented contiguously with or immediately after the response. When this stimulus is withdrawn, response probability is decreased.

A reinforcing stimulus may be presented in three ways:

1. Externally and transmitted to the central nervous system via external receptors, e.g., food, music, smiling, praise, etc.

2. By direct stimulation of the central nervous system bypassing the external receptors.

3. By instructing the patient to initiate mediational processes such as thinking or imagery. It is assumed that stimuli which act as representatives of external stimuli (imagery) can be, under certain conditions, functionally equivalent to the stimuli presented by the other two methods.

A crucial assumption is that the manipulation of covert processes can influence overt processes in a predictable manner. There is some support for such an assumption. In the covert reinforcement procedure both the response and reinforcing stimulus presented in imagination are made as similar as possible to the external response and stimulus. It is assumed that on the basis of stimulus-response generalization there will be a transfer to conditioning from imagination. Though this assumption remains to be experimentally verified, there is ample evidence that both stimulus and response generalization occur.

Investigators in behavior therapy are providing evidence that manipulation of imagery and other covert processes can modify maladaptive behavior.

The successful use of such procedures in imagination has led me to speculate on the possibility of presenting a reinforcing stimulus in imagination in order to influence behavior in a manner similar to the external presentation of reinforcing stimuli. This procedure is labeled covert reinforcement. The term "covert" is used because the response and the reinforcing stimulus are presented in imagination. The term "reinforcement" is used to indicate that the purpose of the procedure is to increase response probability. The description of the method has been limited to the modification of maladaptive behavior, but in principle is applicable to all behavior influenced by learning.

General Description of Method

Discovery of possible reinforcers—After it has been determined from the usual behavioral analysis of a patient that covert reinforcement is indicated, the first step is to discover possible reinforcing stimuli. Three possible sources are utilized: The main source of identifying reinforcing stimuli is the Reinforcement Survey Schedule (RSS) which is administered routinely as part of the behavioral analysis. The RSS is composed of 54 items and is divided into four primary sections: reinforcers which can be presented in palpable, facsimile, or imaginary form; reinforcers which can be presented only in facsimile or imaginary form; situa-

---

Condensed with permission from *Behavior Therapy*, 1(1):33–50, 1970.

tional contexts which may be reinforcing; and a survey of frequently occurring daily behaviors. In the first three sections the respondent rates each item on a 5-point scale according to the degree to which he feels enjoyment or pleasure for it.

After the patient has completed the RSS, the items to which he attached "very much" responses are rank ordered by him, ranging from the least pleasurable to the most pleasurable items. The first three items so ranked are then tested for possible presentation as reinforcing stimuli. The procedure of using the patient's high preference items for reinforcing stimuli is based on data which indicate that the quality of reinforcement influences the effectiveness of a reinforcer.

In order to test the item for its reinforcing qualities, the patient is asked to close his eyes and imagine receiving the stimulus, e.g., if the item selected is rock and roll music, the patient is instructed in the following manner:

> Choose your favorite rock and roll song, and try to imagine you can really hear it. As soon as you feel you can really hear it clearly, signal me by raising your index finger.

After the patient signals, the therapist inquires about the clarity of the stimulus. If he affirms that the stimulus was imagined clearly, the trial is repeated and the same question is asked.

The item is included as a reinforcing stimulus if the following criteria are met: The patient perceives it as desirable, pleasurable, or enjoyable; the patient is able to obtain a clear image of the stimulus; the patient is able to obtain the image almost immediately after its presentation, i.e., within 5 seconds.

The second method of determining possible reinforcing stimuli is by asking the patient to suggest other events or items not on the RSS which would be pleasurable for him.

Further information can be derived from case histories, relatives, friends, and ward personnel. This source is utilized with patients who report few pleasures in life and label few items in the "very much" column of the RSS.

It is important to have a number of possible reinforcers available for each patient so that satiation will not occur.

Description of Procedure

When COR is used it is not necessary to teach the patient to relax, nor is it necessary to construct a hierarchy as in the desensitization procedure. A typical example of the application of the technique is presented below.

A male subject treated for homosexuality, who had lost sexual urges toward males by the use of covert sensitization, was reluctant to call a girl for a date. He was instructed as follows:

> I am going to ask you to try and relax and close your eyes. Then I will describe a scene to you. When you can imagine the scene as clearly as possible, raise your right index finger. I will then say the word "reinforcement." As soon as I say the word "reinforcement" try to imagine the reinforcing scene we practiced—the one about your swimming on a hot day, feeling the refreshing water, and feeling wonderful. As soon as the reinforcing scene is clear, raise your right index finger. Remember to try to imagine everything as vividly as possible, as if you were really there. All right, now close your eyes and try to relax.

The therapist then presents a scene such as:

> Imagine that you are home and you say to yourself, "I think I'll call Jane for a date." When you have that scene clearly, raise your finger. (As soon as he raises his finger, the experimenter says, "Rein-

forcement.") Was the delivery of the reinforcement clear? After you've decided to call Jane, you walk toward the phone and start dialing. Raise your finger when this is clear. ("Reinforcement.") Now you have finished dialing. Jane answers. You say, "Hello" and ask her if she is free Saturday night and tell her that you would like to take her out. Raise your finger when this is clear. ("Reinforcement.") Now do the whole procedure yourself. Imagine you decide to call. Deliver a reinforcement to yourself, then imagine you are dialing, then deliver a reinforcement to yourself. Imagine you are asking for a date and deliver a reinforcement to yourself. When you are all finished, raise your right index finger. Make sure you get clear imagery. You can see and feel the phone, etc. Try to imagine that you are comfortable and confident while you are in the kitchen going through the procedure. All right. Start.

After the patient has practiced the entire sequence, he is told to practice twice a day at home, doing the procedure two times each practice session. He is urged to try to actually make the call and when he is about to call, he is told to deliver the reinforcements to himself at the same places he did in imagination.

This procedure is now employed with every patient I see, and is supplemented by other standard behavior therapy procedures. For example, if a client is having difficulty asserting himself, he is given scenes in which he is asserting himself and is covertly reinforced for that behavior. In each session, the patient is given 5–10 trials on each response to be increased. The patients are given homework in which they are told to practice the procedure once or twice a day, depending on the patient's motivation, the strength of the response to be changed, and the immediate necessity to change the response. The therapist has to be careful in choosing the reinforcement. Patients differ on clarity of imagery depending upon the sensory modality employed. Some patients can vividly imagine that they are eating their favorite foods; other clients who may report great pleasure in eating certain foods are unable to feel the taste of the food in their mouths when asked to imagine it.

Parameters of Covert Reinforcement

The labeling of this procedure as covert reinforcement makes available the general body of knowledge concerning reinforcement. Such knowledge can be utilized to maximize the efficacy of covert reinforcement. In the application of the covert reinforcement procedures, we have attempted to control five parameters that investigators agree influence reinforcement. They are: the number of reinforcements, intertrial interval, immediacy of reinforcement, schedules of reinforcement, and drive state.

Number of reinforcements—The strength of conditioning increases as a function of the number of reinforcements. Therefore, we give as many trials as possible of COR in the consulting room.

Intertrial interval—In order to avoid inhibition of reinforcement and too rapid a growth of inhibitory potential, an attempt is made to distribute the trials in the consulting room and at least a minute between trials. The patients are instructed to practice at different times during the day, allowing at least a minute between trials.

Immediacy of reinforcement—Responses which are followed immediately by a reward are learned more rapidly than responses for which the reward is delayed. As a result patients are instructed to switch immediately to the reinforcing scene when the therapist says, "reinforcement."

Schedules of reinforcement—The

goal of the procedure is to achieve a high rate of responding and increase resistance to extinction. Operant literature has amassed many data demonstrating that partial reinforcement leads to higher response rates and greater resistance to extinction than 100 percent reinforcement. In applying COR, a 100 percent reinforcement schedule is used at first. After there is evidence that the desired responses are being increased, the ratio of reinforcement is increased in successive steps.

Drive state—Operant investigators also manipulate deprivational states to increase the effectiveness of reinforcers. Although this variable is difficult to manipulate in the clinical setting, attempts have been made to do so, e.g., if a client is using an eating response as a reinforcing stimulus, he is encouraged to practice before meals; if he is using a swimming scene as a reinforcer, he is asked to practice when he feels especially hot.

Problems That May Arise in the Use of Covert Reinforcement

Poor imagery—Occasionally clients claim that they have poor imagery. This can be overcome by imagery training or by examining the clarity of imagery in all the sense modalities. The therapist should be careful to describe the scenes in as much detail as possible, including as many sense modalities as possible to increase the probability of transfer to the real situation.

Lack of practice outside the office—Usually this can be overcome by applying the COR procedure itself to scenes of practicing outside the office.

Anxiety and covert sensitization—Some clients who are being treated for maladaptive avoidance behavior report that although they are beginning to approach the feared object, they still experience some anxiety in doing so. It is explained that the anxiety will usually extinguish because the avoidance response is not reinforced in that the anticipated danger does not occur. A special effort is made to have them imagine that they feel comfortable and happy while they are imagining the scene to be reinforced. By the time treatment is terminated, the patients seldom report the least amount of anxiety.

Possible spontaneous recovery or reconditioning after treatment—The usual procedure is to produce overlearning by continuing treatment for at least six sessions after the maladaptive behavior has been eliminated.

I believe that COR is a powerful tool for behavior modification for a number of reasons:

The application of other behavior modification procedures such as desensitization based on relaxation, implosive therapy, and covert sensitization have received experimental confirmation of their efficiency in the modification of maladaptive behaviors.

There is nothing in the writings of learning theorists such as Pavlov, Hull, and Guthrie to contradict the effective use of imagery in behavior modification.

The procedure has produced desired changes in a variety of behaviors. Often, in fact, when other behavior modification procedures have been slow to bring about results, or have been ineffective, the use of the COR procedure produces the desired behavior.

A Retrospective Study of Case Attrition in a Child Psychiatric Clinic

RICHARD L. COHEN and CHARLES H. RICHARDSON

Our sample of attrition cases was obtained by selecting serially the last 250 dropouts from the caseload of the outpatient clinic of the Children's Service of the Nebraska Psychiatric Institute. In addition, 100 control cases were selected at random. A control case was one in which attrition did not occur. Eighty-three of the original 250 cases did not meet the definition of "attrition" and these were eliminated, leaving 167 cases.

Inspection of the data suggested that we were dealing with two types of case populations. Cases terminated during the intake or diagnostic phase are conceivably characterized by a unique constellation of factors in contrast to those cases terminated during the treatment phase. We, therefore, dealt with these two subgroups as separate caseloads within both the experimental and control samples. Of the 167 experimental cases, 126 were in the pretherapy subgroup and 41 in the therapy subgroup. Of the 100 control cases, 74 were in the pretherapy subgroup and 26 in the therapy subgroup.

The 350 cases of the original sample were read and scored independently by three raters using a protocol containing 40 separate items. Of the 40 items, 22 involved objective reporting of factual data from the chart. These items included:

Age, sex, race, religion, type of school, grade in school, distance from clinic, parent constellation, family income, number of siblings, birth order, source of referral, time elapsed between initial contact and ongoing service, time elapsed between initial contact and last contact, time elapsed between last contact and closing, presence of followup, staff turnover, number of trainees assigned to case, total number of interviews, total number of visits, incidence of reapplication for service, type of presenting complaint.

In addition, the raters made 18 judgments concerning the referral source, the family and child, and the clinic itself, as follows:

Observations related to referral source—Error in diagnosis with inappropriate referral; failure to explain nature of service and properly prepare family (including coercive referrals); ambivalent referral—mixed signals given to family concerning value and competency of service; "dumping" referral—desperate move following one or more unsuccessful attempts at treatment; gross ignorance or lack of sophistication concerning indications for service.

Observations related to activity of family and child—Grossly inappropriate parental motivation; family overstressed by multiple demands and unable to persist in treatment efforts for child; flight from other professional advice in which child was diagnosed as needing a type of treatment unacceptable to both parents (or as irreversibly damaged; shopping); gross ignorance or lack of sophistication concerning nature of service offered; insufficient interest in or investment in the rearing of this child; flight into health.

Observations related to activity of clinic staff—Failure to make proper "diagnosis" early enough; failure to apply previously established intake criteria; breakdown in supportive relationship with family because of lack

Condensed with permission from *Social Psychiatry*, 5(2):77–83, 1970.

of continuity of care; failure to resolve collaborative problems between clinical team members; misassignment (e.g., one or more professional people on case too inexperienced for complexity of problem); failure to assess true nature of motivation of parents and child in seeking care; excessive wait for service.

There were three factors which appeared to differentiate attrition from control cases for both the pretherapy and therapy subgroups. In both subgroups the staff tended to keep attrition cases on an "open" status longer and to make greater efforts at followup (apparently unsuccessfully); and, that the parents had "insufficient interest or investment in the rearing of this child." Apparently, despite efforts to bring some dropout families back into the clinic, the parents could not or would not respond.

The typical pretherapy attrition patient tends to have parents who were not only insufficiently invested in the child's care but often came to the clinic with inappropriate motivation, little knowledge concerning the nature of the service offered, and tended to be symptom oriented. This last observation is related to the difference between the two groups in which termination could be attributed to "flight into health."

Our finding that attrition rates are higher in intact families where the child is living with his natural parents may be related to the fact that, for many such parents, the clinic experience carries with it projections of accusation by the staff. Natural parents display more guilt in relation to unfavorable development in their children which would make them more sensitive to the historical, exploratory interviewing that typifies the intake period.

The finding which indicates higher incidence of presenting complaints of the affective type in the pretherapy attrition cases is difficult to explain. One possibility is that these are more likely to show "spontaneous" improvement and may be more prone to use flight-into-health defenses.

Another finding in the pretherapy subgroup which permits only speculation is the higher incidence of "incorrect diagnosis" among the control cases. In any event, the diagnostic acumen of the referring person did not seem to be a crucial contributing factor to case attrition.

The referring source was important in terms of how well it prepared the family for what services the clinic could perform and how it went about performing them. Failure to prepare a family adequately for the clinic experience, or referral recommendations that were perceived by the family as coercive proved to be contributory toward high attrition rates.

Families who were required to wait long periods of time for service tended to drop out at a higher rate than those who were not. Some parents reacted as if they had been rejected and developed negative attitudes toward the clinic. In some instances it would appear that during the long wait the family's adaptive mechanisms came into play and there was resolution of the problem so that with one or two interviews, there was no longer the need for help. Some families were surprised that they were considered "dropouts" because they believed that they had been helped and felt quite positively toward the clinic.

There was only one instance of difference between the attrition and control in the therapy subgroup: there is a greater incidence of antisocial behavior as the presenting complaint in the attrition sample. This seems more understandable than the

higher occurrence of affective symptoms in the attrition sample of the pretherapy subgroup. Children and adolescents with antisocial behavior usually prove to be difficult or explosive treatment cases. Their behavior is the most intolerable to the community and if treatment results are not forthcoming, other pressures may be brought to bear on the family to seek other intervention. Since most of these parents themselves harbor a core of psychopathic attitudes toward authority, they would be more likely to handle separation from the clinic irresponsibly rather than through mutual arrangement. Also, many of the parents of these children have been coercively referred and are comfortable with the child's behavior themselves. They tend to drop out in greater numbers because they are more comfortable with the child's behavior than the school and community are and do not see any problem.

The study failed to confirm several theories concerning the reasons for case attrition. The theory that families who live long distances from the clinic are more likely to drop out at a higher rate was not confirmed. Race and levels of family income failed to differentiate attrition from control cases. The theory that high staff turnover in cases tends to make families discouraged was not corroborated nor was the commonly held belief that large numbers of trainees make for higher attrition rates. The contention that some referral sources refer "better" cases than others was not confirmed.

Recommendations for future studies would emphasize: Projects of this type should be prospective in nature rather than retrospective. A larger sample of experimental and control cases should be used. An independent team which has no clinical responsibilities for management of the project sample itself should be active in the clinic *during* the period in which cases are actually being seen.

Definitive recommendations related to changes in the pattern of services should await studies of the type recommended above. Several suggestions warrant emphasis.

Considerable time should be invested with the parents in an exploration of their conscious and unconscious motivations in coming for service, degree to which they are symptom oriented, historical and current nature and degree of investment in the rearing of *this* child, and what they understand about the role and function of a child psychiatry clinic.

Special effort should be made to establish lines of communication with referral sources. Constant feedback about the progress of the case may insure more support of the clinic in future referrals.

Perhaps every clinic should have a "crisis team" which can be available within 24 to 48 hours of initial contact to see cases in which there is strong possibility that decompensation is taking place at a rapid pace in the family. Placing families of this type on a waiting list is tantamount to offering no service at all.

There is some suggestion that the open-ended nature of psychiatric service tends to be threatening and frustrating to some parents. It may be helpful to many families to structure the service, to give it a time-limited design, and to indicate that mutual reassessment will take place at certain milestones which will permit the family to reformulate its decision before committing itself to any further action.

The Intelligence of Children of Schizophrenics

ELLEN A. LANE, GEORGE W. ALBEE, and LYNDA S. DOLL

As schizophrenia is often considered a cognitive disorder, it should be of interest to examine the influence of schizophrenic parents on the intellectual development of their children. The following hypotheses were investigated:

Children of schizophrenics perform more poorly on intelligence tests than their parents did when they were children, long before the diagnosis of schizophrenia.

Children of the same sex as their schizophrenic parents perform more poorly than children of the opposite sex. This hypothesis is related to reports of sex concordance in the development of schizophrenia for children of schizophrenics.

Children with schizophrenic mothers perform more poorly than children with schizophrenic fathers. This hypothesis is related to the general view that mothers have a greater influence on the development of their children.

Names and childhood IQs of schizophrenic subjects and names of their children were available from previous studies. The IQs of their children were located at the Cleveland Board of Education, as their parents' childhood IQs had been located earlier.

Subjects were included if a Kuhlmann-Anderson Group Intelligence Test or a Stanford-Binet score from before the age of 10 years was available for a schizophrenic parent and at least one child. The final group of subjects consisted of 76 schizophrenic mothers with 156 children and 53 schizophrenic fathers with 106 children.

If two tests were available the earlier one was chosen. The mean IQ of children within each family was used so that large families would not unduly influence the results.

Children of schizophrenic parents did not score lower on intelligence tests than their parents had during childhood. On the basis of raw scores only, children scored significantly higher than their parents. However, because of the regression effect, these children cannot be said to have performed significantly better than their parents; that is, children's scores did not differ significantly from estimated scores obtained from a regression equation based on parents' scores.

Children of the same sex as their schizophrenic parent did not perform more poorly than children of the opposite sex. Daughters did somewhat better than sons in comparison with parents' scores whichever parent was schizophrenic, suggesting the usual finding that girls perform better than boys during elementary school. Again, the significant difference that was found between the raw scores of daughters and their schizophrenic parents was not substantiated when the regression effect was taken into account.

Children of schizophrenic mothers did not perform more poorly on intelligence tests than children with schizophrenic fathers, in comparison with their parents' early scores. Indeed, the performance of children of schizophrenic mothers was better than that of children with schizophrenic fathers when the intelligence of the nonschizophrenic parents was also considered.

Condensed with permission from *Developmental Psychology*, 2(3):315–317, 1970.

Population and Sample: A Major Problem in Psychiatric Research

J. B. Chassan

Suppose one is involved in a drug trial in which patients are randomized into two subgroups, one in which each member receives the test medication, the other in which each receives a placebo. The sample consists of the patients in the study; the population of reference is the larger group of patients, the so-called "hypothetically infinite population" of patients. This is the population about which inferences concerning the drug are to be made. In theory the sample is to be regarded as having been randomly selected from the population. Such random selection is an idealization, because any population of humans (or real objects of any kind) must be finite, which is why we speak of *hypothetically* infinite populations.

Since one cannot obtain a random sample from a hypothetically infinite population, one must be satisfied with a random-in-effect sample. This implies that the sample is an adequate representation, in some sense, of a process which would give rise to a well-defined infinite population. The results obtained from the sample are then generalized within a probability framework to the corresponding hypothetically infinite population. Next one applies the inference about the hypothetical population to actual subsequent samples, as in the treatment of particular clinic patients. In theory, the latter must represent random samples from the same population if the inference is to be valid.

To summarize, we first perform an experiment in which we compare two treatments for their relative worth in terms of some effect that we are looking for. Treatment A turns out to be significantly better than treatment B for some condition, C. These results are generalized to the hypothetically infinite population: a greater proportion of individuals in the population would be successfully treated for condition C by A than by B. Then, when confronted by individuals with the condition C, A is administered in preference to B.

Before we proceed to the problem which this model poses, it will be useful to discuss the concepts of the hypothetically infinite population and that of a random or random-in-effect sample drawn from such a population. The connection between the two concepts is basic to the understanding of either.

First, when one speaks of a hypothetically infinite population in statistics, one has the idea of an indefinitely large aggregate of objects, things, or people—more specifically, some identifiable quality and/or quantity associated with each member of the aggregate. Although the quality or quantity will vary from one member to another within the aggregate, there is a requirement that there exist a uniformity, or a homogeneity, among the members. This sounds contradictory. It's easy to understand that one has to deal with variability wherever statistics or statistical analysis is concerned. The more difficult question has to do with homogeneity.

Take a group of patients newly admitted to a State hospital, each with a diagnosis of schizophrenia, and, as

Condensed with permission from the *American Journal of Orthopsychiatry*, 40(3):456–462, 1970.

a statistic, consider the percentage of these patients discharged within a year. Let us say that this percentage is 60. Next, we may want to consider this group of patients as a random-in-effect sample of a hypothetically infinite population of similar schizophrenics with respect to the question of discharge within a year following admission. The variability from one to another member of the population as well as of the sample is determined by whether or not discharge from the hospital takes place—within a year following admission. But what about homogeneity, or uniformity? A facile answer might be that the homogeneity of the sample, and therefore of the hypothetical population from which it was randomly-in-effect selected, is determined by the fact that the members were defined as newly admitted schizophrenics to the State hospital. What this means technically is that the probability of discharge within a year is constant from patient to patient. Now this in itself cannot mean much because the probability of an occurrence insofar as its usage in statistics is concerned is defined in terms of the percentage of times the occurrence takes place out of the total number of opportunities for it to take place. Thus, the 60 percent discharge rate may be regarded as an estimate of the probability of discharge in the infinitely large hypothetical population—the probability representing a percentage of patients discharged.

So we get back to the question of interpreting the meaning of a probability as applied to a single patient within the sample. To do this we have to consider the particular attributes of the patient which seem relevant to improvement, and theoretically consider the patient as one member of a hypothetically infinite population defined by those attributes. Let us suppose that the probability of improvement in such a population would be low. We could justify this estimate, for example, where we are dealing with a regressed hebephrenic who has been hospitalized continuously for 20 years from the age of 40.

Let us assume that most of the rest of the patients in the sample are new admissions diagnosed as schizophrenic and between the ages of 30 and 35. These patients would be expected to have a more favorable prognosis than the hebephrenic. It doesn't take much understanding of probability theory and the philosophy of statistics to recognize that the hebephrenic does not belong in the sample. To the extent that he and others like him are present in the sample, the sample may be said to lack homogeneity. From a more technical point of view, we are not dealing with a random, or random-in-effect, sample from a well-defined hypothetically infinite population, the reason being that the statistical parameter under investigation cannot be considered as equal for all patients in the sample. All tests of significance and associated probability levels, etc., depend upon the assumption that the data are random or random-in-effect. To the extent that this random quality is lacking, statistical inferences drawn from such samples may be fictitious and, in fact, misleading.

The total sample need not necessarily be homogeneous in this sense. As long as essential prognostic differences in a total sample between patients are recognized, the data can be handled in a way such that, in theory at least, the analysis can be valid. One approach is by subgrouping the total sample into homogeneous subsamples corresponding to respective populations. The pairing of patients represents an attempt to sub-

tract out prognostic differentials. But one trouble with subgrouping techniques is that the sample usually is not large enough to allow for adequate subsample sizes. It is very difficult to base the pairing on more than a limited number of characteristics.

Let us consider a hypothetical study involving 40 patients, 20 randomly assigned to drug A and 20 to placebo. Let us consider that the 40 patients all have some assumed favorable prognosis, say that of 85 percent on the medication and 45 percent on placebo, and that these percentages were actually obtained: that 85 percent of 20 improved on the active drug, and 45 percent of 20 improved on placebo. This difference would be significant at the .01 level.

Let us next assume that of the 40 patients, 37 are homogeneous in the sense described above, with the relatively favorable prognosis, such that they each possess an 85 percent true probability of improvement on drug A and 45 percent on placebo. Let us also assume that the remaining three patients each have a poor prognosis as indicated by a mere 10 percent true probability of improvement, irrespective of treatment.

Suppose that in the randomization procedure all three patients with the poor prognosis wind up in the same group, say the group on drug A. We can then make the assumption that none of these three patients improved, so that instead of 17 out of 20 improvements on the drug, there would then be only 14—against the 9 on placebo. This result would then fall short of statistical significance. This is a simple illustration of how a heterogeneous sample can fail to demonstrate a true effect. It is also possible for a heterogeneous sample to bias the data toward an apparently statistically significant effect when no true difference exists. Heterogeneity, or a lack of randomness, is not always that obvious. It is often wrongly assumed that the randomization process ensures at least a comparability between groups, if not a homogeneity within each group.

In the example the bias resulting from heterogeneity was rather apparent. But there was also the possibility of more extensive heterogeneity and lack of randomness. The consideration of additional heterogeneity or lack of randomness or of bias was ignored because of our assumption of a fixed probability of a favorable prognosis on a given treatment within each of the groups. This is the kind of assumption which is open to question if one recognizes the differences that can exist between psychiatric patients of the same diagnosis and with apparently similar other characteristics.

The larger the sample, the greater the probability for such a balancing. However, the problem of securing a reasonably clear definition of the hypothetically infinite population which the total sample is theoretically drawn from becomes correspondingly more severe. The situation is somewhat as follows: The hypothetical infinite population must be considered as an ad hoc extension of the patient sample. Then, the patient sample has to be heterogeneous with respect to at least some factors such as age, educational level, family structure, childhood experiences, treatment history, marital status, etc., as well as relevant physiological, intellectual, genetic, socioeconomic variables, etc. The population of reference then becomes vague, being a mixture of unknown proportions of component populations. In practice, if we say we have obtained statistical significance favoring a test medication over placebo,

how is this result to be applied in the treatment of patients? The situation can be appreciated if we consider another hypothetical example.

Suppose we have two groups of 20 patients each, with one group randomly selected for test medication and the other 20 for placebo. Again, we shall use the percentage of patients improved as our measurement of efficacy. Suppose the number of patients who improved on placebo was 10. It would then take 16 out of 20 improvements on the test medication to reach the .05 level of significance. If only 15 instead of 16 improved, we would say that there was not enough difference in improvement percentages to assert that any of the patients on the test medication benefited beyond the placebo effect. But if 16 or 17 instead of 15 improved on the medication as against the 10 on placebo, we might say that at least one or two patients in the medication group must have benefited at least in part as a consequence of a true psychopharmacological activity of the medication. Of course, this conclusion can be erroneous if the total sample was not homogeneous and if there happened to be a bunching of atypical cases in one of the groups.

Suppose that there was a negligible bias despite a lack of overall homogeneity in the data. That is, assume that the distribution of patients into the two treatment subgroups was such that there was a reasonable balance of prognostic characteristics between them. Consider the interpretation under these conditions of a result which gives rise to 17 out of 20 patients improved on the medication and 10 out of 20 on placebo. This implies that at least some patients on the medication benefited through the psychopharmacological activity, of the drug, as distinguished from those within the test medication group whose response may have been on a placebo basis as were the 10 improved cases in the placebo group. When a statistically significant effect is obtained, it does *not* necessarily follow that a large proportion of the patients on the medication benefited because of the psychopharmacological properties of the drug. A true pharmacological effect could have been present in as few as one or two cases!

The question becomes in which cases with which characteristics, did the true drug effect occur? This question cannot be answered. From a technical statistical point of view the problem is that of having to make an inference to a population which is necessarily an ad hoc extension of a heterogeneous sample.

The usual type of statistical model applied to drug research in clinical psychiatry is a rather weak scientific instrument for attempting to arrive at reasonably specific indications for drug usage, and other approaches ought to be considered. One approach, when feasible, involves the application of statistics to the detailed study of individual cases, as in the testing of hypotheses within patients rather than between groups of patients. This is known as the intensive model of clinical research design and provides an approach toward the specification of patient characteristics in relation to particular drug effects.

Psychosomatic Diseases of the Skin

Joseph J. Eller and Stephen Silver

Some emotional states are related to certain physiologic changes. Dilatation of the pupil with fear and tachycardia with excitement are examples. The most discernible and everyday examples are found in the skin. The skin may be said to be a barometer of emotional states.

One might hypothesize that the skin is related to the psyche on several counts. The epidermis has the same embryologic origin as the nervous system. Second, the skin holds a uniquely important position in our individual cosmologies. It is the shelter which protects us and the facade which displays us. As that part of the person which is visible, it represents ourself to others, whether we like it or not. The skin is a detector and educator, in that it acts as a sense organ for touch, cold, heat, and pain. It is the source of much erotic gratification. Since the skin involuntarily communicates to others some of our emotional states, it may be a source of anxiety.

The classification which follows is from a dermatologic point of view, organized along the lines of cutaneous pathology rather than psychopathology.

Cutaneous Manifestations of Emotional States (Involuntary)

The cutaneous manifestations of emotional states are blushing, blanching, and sweating. Piloerection is another, but is less important.

Blushing and flushing are usually regarded as synonymous. Blushing, usually implies an emotional origin, while flushing implies excitement, stress, and nonemotional causes. The former concentrates on the shiny red quality of the skin, the latter on the sudden rushing quality of the erythema. Flushing may be brought about by increase of body temperature, ingestion of alcohol or caffeine-containing beverages, spicy foods, drugs, endocrine phenomena (e.g., hot flashes), and disease states (pheochromocytoma and carcinoid tumors). Reactive vasodilatation follows exposure to cold. This redness may be brought on, also, by emotional states, such as embarrassment and anger. The phenomenon occurs normally; it is difficult to say at what point blushing becomes abnormal.

Some people blush more frequently than others. Either they experience blush-producing emotions more frequently or their threshold of cutaneous response is lower. In one case, the main pathology would be physiological, in the other psychological. In some individuals, the blush takes the form of discrete red marks on the chest, neck, or face. Often these patients seek medical advice, unaware that this "rash" is simply their mode of blushing. The condition is called *erythema fugatum* and may be produced by ingesting alcoholic beverages. Whatever the cause of episodes of facial vasodilatation, eventually the cutaneous blood vessels may become damaged and enlarged, so that telangiectases become apparent.

The opposite of blushing is blanching. This is caused by cold, physical states, such as shock, and emotional states, primarily fear. Extreme fright causes a generalized discharge of the sympathetic nervous system, part of

Condensed with permission from *Behavioral Neuropsychiatry*, 1(No.11–12):25–35, 1970.

which innervates cutaneous arterioles. This, along with the liberation of epinephrine, causes these blood vessels to constrict. Although some people blanch more easily than others, there are no abnormal variants of this phenomenon. Nor are there abnormal variants of piloerection which is brought about by the same stimuli which produce blanching.

The only gland in the skin responsive to emotional states is the eccrine sweat gland. These glands are found over the entire body surface and their main function is to regulate body temperature by means of evaporative cooling. The increase in blood temperature is monitored by the hypothalamus which sends impulses to the sweat glands, via the sympathetic nervous system. Emotional stress may likewise cause sweating, presumably as a result of sympathetic nervous system activity. Not all sweat glands are equally activated. Those of the palms, soles, axillae, and forehead respond more readily to emotional stimuli, although strong stimuli may cause generalized sweating. Emotional sweating is a normal phenomenon. It is considered abnormal if it occurs in an unusual location or is unusually frequent or intense.

Hyperhidrosis usually occurs on the palms and soles, axillae, perianal and antecubital areas, forehead, tip of the nose, and upper chest, although other areas may be involved. A cold and sweaty palm is the hallmark of this condition. Hyperhidrosis is related to stress, whether it be fear, pain, or nervous tension. At times, it may appear to be constant, although it does not occur during peaceful sleep. Profuse sweating on disrobing is called "hyperhidrosis nudorum." The fact that these patients usually also sweat profusely in hot weather and that the ingestion of pilocarpine causes an exaggerated sweating response suggests that the site of pathology lies in the overresponsiveness of the sweat glands. There may be a familial history of the condition.

Dyshidrosis (pompholyx) was originally believed to be caused by bubbles of sweat being trapped in the skin of the palms and soles. Pinhead-size, deeply seated vesicles are scattered on these areas, particularly along the sides of the fingers. Most patients have only palmar involvement. Itching may be severe, lasting until the vesicles rupture usually several days after their appearance. Remissions and exacerbations may go on for years. Often, attacks are precipitated by psychological stress. Although it is now apparent that the vesicles are eczematous in origin, this condition occurs more frequently in subjects who have hyperhidrosis. It is likely that dyshidrosis is an eczema aggravated by secondary sweat retention.

Cutaneous Manifestations of Neuroses, Psychoses, and Nervous Habits (Self-Induced)

Bona fide skin diseases with no emotional basis occur in mentally disturbed individuals. Any skin lesion may become a focus for the habit of picking or rubbing, and a secondary self-induced lesion is formed. If there is no preexisting dermatosis but the patient acts as if there were, then the behavior is due to a compulsive habit or a more severe form of psychopathology. The following conditions occur in emotionally disturbed individuals. Nearly all are self-inflicted.

In "neurotic excoriation" there is nothing wrong with the skin, yet the patient digs into it with his fingernails to remove some actual or imagined tiny skin blemish. The patient usually discovers the "blemish" by inspection, rather than by any "symptom" it

produces. The excoriations are usually deep enough to leave hypopigmented scars. The patients are unable to refrain voluntarily from this self-mutilation. Tendencies toward this behavior may be noted in those patients who aggravate preexisting skin conditions by overtreatment or overcleanliness. Although these patients realize that they are aggravating their dermatoses, they persist in their behavior.

A special form of neurotic excoriation is "acne excoriée de jeunes filles." Nearly all cases of acne lesions are occasionally picked or squeezed by the patient. Some sufferers "interfere" with their acne more than others. The acne itself is mild or even nonexistent, but there is evidence of harsh picking and self-mutilation.

Related to neurotic excoriations are two conditions in which self-destructive impulses are directed at the hair or nails. Trichotillomania refers to the desire to pull out one's hair. In children, it is usually self-limited. In adults, it may be a manifestation of psychosis. Eyebrows, eyelashes, axillary, and pubic hair may be involved. Onychotillomania, the impulse to tear out the nails, is extremely rare, but less destructive habits involving the nails are quite common.

Many skin lesions result from compulsive movements that are more or less destructive. The most dramatic are seen in mentally defective and psychotic patients. Biting and chewing of the skin produces area of erythema and hyperkeratosis and, eventually, hyperpigmentation and excessive hair growth. The cutaneous manifestations of nervous habits in normal individuals are numerous: Nail biting is perhaps the most common. Thumb sucking in children may lead to severe chronic paronychia and nail deformity. Individuals who lick their lips develop dry, scaly lips which may develop fissures. A habit of scratching the surface of the thumb nail with the nail of the index or middle finger of that hand produces a characteristic furrowing of the thumb nail. Excessive handwashing leads to excessive dryness and irritation of the hands, as well as paronychia.

Factitial dermatitis is the term applied to any self-inflicted skin injury in which the patient denies that he has produced the lesions. Some patients are unaware of having injured themselves. Others are malingering. They use the lesion for secondary gain—to explain failures, win sympathy, escape responsibility, or simply to keep up the flow of disability payments. In either case, this differs from the patient with neurotic excoriation, who readily admits to having produced the lesions himself. Patients with factitial dermatitis utilize a variety of injurious substances, such as caustic chemicals and pointed objects. The bizarre appearance of these lesions is characteristic. Any lesion usually appears suddenly and full-blown at the onset. If the lesion is wrapped in an occlusive dressing so that the patient cannot get to it, it will gradually heal. Dermatologists realize that it is unwise to confront the patient with the diagnosis.

Phobias and delusions referable to the skin may not have any outward manifestations. The phobia that most frequently brings a patient to the dermatologist is parasitophobia. But the delusion of parasitosis, in which the patient believes himself to be infested with parasites, is more common. Some patients with this complaint show no outward evidence of it; others demonstrate excoriations and other forms of skin injury. Parasitophobia carries a less serious prognosis than the delusion of parasitosis. It is up to the dermatologist to rule

out actual infestation; further management belongs to the psychiatrist.

Syphilophobia, though rare, still exists. Men are more often affected than women. Cancerophobia is more apt to occur in older individuals who have had cancer or who have a close relative or friend with the disease. These patients are extremely concerned about the possible malignancy of the tiniest blemish. Rather than trying to convince these patients of the benign nature of the lesion, it is better to remove it and have it examined for malignancy. Bacteriophobia is related to mysophobia, the fear of being dirty. These patients bathe too frequently which leads to generalized xerosis and pruritis. Too frequent handwashing, and in some cases, the use of disinfectant chemicals leads to chronic dermatitis of the hands. Bromhidrosophobia is the fear of body odor. The complaint is not related to the actual strength of the patient's body odor and, unlike true bromhidrosis, the treatment is psychiatric. Ereuthrophobia, or a fear of blushing, is a compulsive state usually seen in women, particularly those who blush easily.

There is a form of hypochondriasis which brings patients to the dermatologist—the unrealistic fear of not looking attractive. It is difficult to say at which point such fear becomes unrealistic, but when a woman is preoccupied with the "unsightliness" of her "enlarged pores," something is amiss. The cosmetics industry has done a great deal to foster this dissatisfaction with one's appearance. Until recently men were concerned with thinning hair, but one may expect that they will become increasingly concerned with moles, acne scars, and "enlarged pores."

Another class of cutaneous manifestations of mental disorders are hysterical symptoms of cutaneous anesthesia and parasthesia. These are extremely rare. A clue to their psychogenic nature is that the symptoms are not correlated with any particular dermatome.

Cutaneous Diseases which May be Incited or Aggravated by Emotional States (Involuntary)

A number of skin diseases are thought to be influenced by emotional states. Stress may precipitate attacks of these diseases or, in chronic conditions, the course of the disease may be adversely affected by stress. The mechanism remains unknown. It was believed that personality types were associated with certain skin diseases. This has been shown to be incorrect, save for that personality type associated with atopic dermatitis.

These diseases may be divided into two groups—those in which emotional factors are frequently involved and those in which they are not as frequently involved. These conditions are skin diseases in and of themselves. They can be activated or aggravated but not caused by emotional factors.

Cholinergic urticaria stands in a transitional position between the first category and this one. Raising the body temperature leads, via a pathway in the central nervous system, to the liberation of acetylcholine at sympathetic nerve endings at sweat glands. This acetylcholine liberation is normally induced by environmental heat, physical exertion, eating hot or spicy foods, or emotional stimuli. Certain individuals are allergic to this acetylcholine and respond by producing a tiny but itchy hive. The lesion begins as a red macule 2 to 6 centimeters in diameter, on which soon appears a pale wheal 1 to 3 millimeters in diameter. These wheals last for several minutes or hours. Blotchy erythema may appear without the wheals. Stress, particularly embarrassment,

provokes attacks. Occasionally, attacks are severe and may be associated with angioneurotic edema, abdominal cramps, diarrhea, weakness, flushing, and salivation.

The ordinary variety of urticaria may rarely be elicited by emotional stress. Although in acute cases, it is usually not too difficult to identify the causative agent, it is rare to find a specific etiology in chronic cases. To classify a case of urticaria as "psychogenic," its appearance should have a definite relationship to emotional stress.

Angioneurotic edema is a variant of urticaria, in which the subcutaneous tissues, rather than the dermis, are involved. The name of the condition derives from earlier theories of its causation and has nothing to do with neuroses. Psychogenic influences may precipitate attacks.

Like urticaria, pruritis has many causes. Among the causes, dry skin (xerosis) is the most common. Other causes are pregnancy, hepatic disease, internal carcinoma, and blood dyscrasias. All forms of pruritis are intensified by emotional stress, but generalized pruritis of psychologic origin is rare. Characteristically, the intensity of the itching is related to the degree of emotional stress, but it is rarely severe enough to prevent sleep. The words the patient uses to describe the sensation may also be indicative of a psychologic origin.

More often, psychogenic itching is localized to a particular region, which may have psychologic significance to the patient. Particularly troublesome is ano-genital pruritis—pruritis vulvae in women and pruritis ani, which affects mostly men. Many cases of itching in these areas are due to dermatologic conditions—psoriasis, scabies, contact dermatitis, and mycotic infections. Infestation with pinworms may be a cause in children.

Pruritis vulvae may be due to lichen sclerosus et atrophicans, or leukoplakia, but is rarely seen in the common benign forms of senile or primary vulval atrophy. Vulvo-vaginal infection with monilia and, occasionally, trichomonas are other causes. Sexual and social factors are important in accentuating vulvo-vaginal itching and they may occasionally be the underlying cause. Scratching the area may be viewed as masturbation or attempted self-mutilation. Often there is a history of disturbed emotional development. Those afflicted tend to be neat, prudish, and immature and have difficulty in marital adjustment.

Pruritis ani may be caused by anal fissures, perianal comedonosis, or hemorrhoids, as well as the dermatologic conditions mentioned above. Contributory psychogenic factors are often important. The condition afflicts mostly men who are obsessional or compulsive; latent homosexuality, or guilt arising from it, is thought to be another factor.

Just as the "pain threshold" varies, so there is a variable "itch threshold." The intensity of the sensation and the reaction to it are determined by psychological factors. Anxiety aggravates itching, much as it intensifies pain. Some patients may complain of itching, yet show no evidence of responding to the stimulus. Usually, patients respond to itching in several ways. The fingers are used to scratch, rub, pick, pinch, or knead the skin. Hairbrushes or rough towels may be used to relieve itching. Other ends, not as apparent, may be served, such as displaced sexual gratification, the satisfaction of masochistic impulses, the relief of tension by neuromuscular exercises, or the expression of shame, guilt, or exhibitionist tendencies.

When the skin is scratched, an excoriation results. It is the hallmark of itching, and patients with generalized pruritis may be covered with excoriations. Rubbing results simply in erythema and swelling of the rubbed skin. With persistent rubbing, in some individuals lichenification develops. This phenomenon first appears as small papules which later join to form plaques, called lichen simplex chronicus, or localized neurodermatitis. This is thickened skin due to hypertrophy of the epidermis and underlying inflammation. Skin markings are more salient, there is some superficial scaling, and often hyperpigmentation. It is common on the nape of the neck (lichen nuche, particularly common in women), legs, posterior shoulders, and genitalia. When the scalp is involved, the hair is rubbed off. Lichen simplex chronicus is more common in women, and in Mongoloids than in Caucasians.

Picking the skin leaves firm, rounded pea-size nodules of hyperpigmented skin, often surmounted with a fresh excoriation. This itches so that it is picked off. This kind of response is elicited by discrete small areas of itching, such as that associated with insect bites, and prurigo is often superimposed on them (papular urticaria, lichen urticatus). Prurigo may also be seen in cases of generalized pruritis, such as that due to pregnancy or internal malignancy. Lesions are more apt to occur on the extensor surface of the arms and legs, upper trunks, and buttocks. The lesions are paroxysmally itchy. When the patient is busy, itching is not a problem, but the pruritis recurs when he is less occupied. Women are more often affected than men.

A characteristic lesion is the "dictator's papule." An individual finds a small lesion in his scalp and picks at it. Initially, what is picked at may be a keratosis, wart, or a small crust from vigorous haircombing. The lesion is picked, particularly when the patient is under stress, such as when a businessman is dictating a letter (hence the name). The more he picks, the larger is the crust that is formed. Eventually, a prurigo papule is formed.

A fourth response to pruritis will occur in a minority of people: actual eczematization of the skin. The reaction, a *pure* dermatitis, is similar to that produced by irritating chemicals or allergenic substances and it is called neurodermatitis. Neurodermatitis frequently goes through an acute exudative stage before showing lichenification. It occurs commonly as a complication of other itching dermatoses, but may occur as an entity sui generis, atopic dermatitis (disseminated neurodermatitis).

Individuals are considered to be atopic if they have hay fever, asthma, or a particular type of eczema, or if there is a family history of these conditions. The type of dermatitis is so characteristic that an individual, whose family history is unknown and who has neither asthma nor hay fever, may be said to be atopic on the basis of the eruption. In infants, the most characteristic feature is itching; in childhood through adulthood, the most characteristic features are its pruritis and its distribution. The popliteal and antecubital fossae, face, neck, and wrists are the sites of predilection. The skin is very dry. The disease waxes and wanes in severity; acute exacerbation is associated with weeping; the chronic stage is characterized by lichenification. The skin is sensitive to itchy stimuli, such as wool clothing or sweat retention in hot weather. Most of the signs of the

dermatoses are due to the patient's scratching and rubbing.

The itch-scratch cycle plays an important role. When the skin is scratched, the area surrounding the scratched spot develops a lowered itch threshold so that itching is elicited by stimuli that would normally be subliminal. As the relief provided by scratching fades away, it is replaced by itching which leads to further scratching. A number of abnormalities, particularly immunologic (elevated gamma K globulin) and enzymatic (increased binding of catecholamines in the skin) have been implicated in the etiology of atopy. Nevertheless, emotional factors are important in determining exacerbations of the disease. Atopic patients tend to fall into a particular personality pattern. They tend to be hyperactive and brighter than normal. Affability and eagerness to cooperate in his dermatologic treatment often belies hidden hostility, feelings of inadequacy, inability to honestly express anger, and emotional lability.

Emotional factors are occasionally important in other diseases:

Seborrheic dermatitis is a common, poorly understood form of eczema, located on the scalp, where it appears as dandruff. The eyebrows, corners of the nose, presternal, and intertrigious areas may be involved. Spread of the disease and increased severity may occur at times of stress. Rosacea may be exacerbated by emotional stress (particularly if stress is sought to be alleviated by drinking). Exacerbations of psoriasis may be occasioned by stress, as may attacks of lichen planus. Some observers feel that these diseases are more apt to occur in individuals who make great demands on themselves. Alopecia areata refers to bald spots on the scalp. The onset may be precipitated by physical or psychological trauma. Herpes simplex is caused by a virus. After the initial attack, usually in childhood, the virus remains dormant, usually around the mouth or on the genitalia. From time to time it reappears as small, painful blisters. These attacks may be precipitated by fever, sun exposure, or emotional stress. Acne is often aggravated at times of stress. Although this usually results from the patient's nervousness, which leads him to pick the lesions, there may be a more direct psychophysiological pathway.

Effects of Cutaneous Diseases on the Psyche

Skin diseases are visible—directly, tangibly. When the skin lesion is on an exposed part of the body, the horror and worry is compounded with the anxiety of having others see it and being the object of pity, disgust, or fear.

Disfigurement is an important determining factor in the emotional effects of a skin disease. The magnitude will be related to the subject's self-image and how he relates to others. Any skin blemish may be the focus of severe emotional problems. Patients may be precipitated into a deep depression by the onset of a skin eruption. One spot of alopecia areata may be a source of great anxiety, if, for example, the patient believes that it represents a loss of virility.

It is to be expected that there is some correlation between the degree of disfigurement produced by the skin lesion and the magnitude of its psychologic effects. Diseases like psoriasis, when affecting the hands and fingernails, can be very disfiguring. Salesmen and others, who have to meet and shake hands with the public, are distressed by this. Pigmenting and depigmenting diseases are apt to create anxiety. Chloasma, more common

since the advent of birth control pills, may be upsetting to young women. Vitiligo among Negroes and other more deeply pigmented individuals may be a serious handicap.

In this country the skin disease which causes more anguish and disability than any other is acne. Teenagers and young adults with severe acne may become withdrawn and depressed. As their acne improves, their outlook brightens and their social life improves. Acne scarring can have a devastating emotional effect on the patient. These scars can be eradicated and even in severe cases, a marked cosmetic improvement can be effected.

Birthmarks are in another category, since their emotional effects start so early. Infants with birthmarks are usually regarded as being different, no matter how much parents and relatives try to disregard the mark. What is worse is that parents may feel, consciously or unconsciously, that the birthmark represents some evidence of their own misdoings, or that they are to blame. These parents may be eager and even insistent that the birthmark be removed. Children tend to be aware of physical differences among themselves and often torment a child who is "different." For that reason, it may be good to remove, when feasible, a birthmark before the child enters school.

Occasionally, a dermatosis may be so intensely and intractably pruritic or painful that it may unbalance the patient emotionally. Acute, painful skin diseases, such as herpes zoster, or a subungual glomus tumor, may be so excruciating and discouraging that the patient considers committing suicide. Dermatitis herpetiformis may seriously impinge upon a patient's emotional stability, as may pruritis ani and pruritis vulvae, in which the itchy sensation is complicated by feelings of embarrassment and guilt.

It is impossible from examining a skin lesion to determine the severity of the mental disorder which led to its production. The dermatologist and the psychiatrist working together will serve the best interest of the patient.

Mental Health News Digests

Implementing the Narcotic Addict Rehabilitation Act

Under the Narcotic Addict Rehabilitation Act of 1966, the NIMH was assigned the responsibility for a nationwide, comprehensive treatment program, including aftercare and supervision of addicts in their own communities. Many local agencies are now providing treatment and rehabilitation under contract to the NIMH. As of June 30, 1970, the following 134 facilities were in the contract program:

DHEW Region I

Department of Mental Health
Bluehills Hospital
Alcohol and Drug Dependence Division
Hartford, Conn.

City of Stamford
Department of Health
Stamford, Conn.

East Boston Social Centers
East Boston, Mass.

Lawrence General Hospital
Rehabilitation Center
Lawrence, Mass.

Marathon House
Providence, R.I.

DHEW Region II

New Jersey Regional Drug Abuse Center
Burma Road, Liberty Park
Jersey City, N.J.

Drug Addiction Aftercare Clinic
Roosevelt Hospital
Metuchen, N.J.

Morris County Aftercare Clinic for Drug Abusers
Morristown, N.J.

Passaic County Narcotic Aftercare Clinic
Paterson, N.J.

Mercer County
Narcotic Addiction and Drug Abuse Program
Trenton, N.J.

Community Child Guidance Center of Camden County
West Collingswood, N.J.

Lincoln Hospital
Drug Abuse Service
Department of Psychiatry
Bronx, N.Y.

Greenwich House Counseling Center
New York, N.Y.

Reality House, Inc.
New York, N.Y.

CISLA
Department of Health
Psychiatric Hospital
Commonwealth of Puerto Rico
Rio Piedras, P.R.

DHEW Region III

Alcoholism Services
Department of Mental Health
Wilmington, Del.

Echo House Foundation, Inc.
Baltimore, Md.

Johns Hopkins Drug Abuse Clinic
Baltimore, Md.

Family Services of Prince Georges County
Hyattsville, Md.

SODAT
Chester, Pa.

Bucks County Psychiatric Center
Penndel, Pa.

Jewish Employment Vocational Service
Philadelphia, Pa.

Harmarville Rehabilitation Center
Pittsburgh, Pa.

George Culmer
State College, Pa.

Alexandria Community Mental Health Center
Alexandria, Va.

Peninsula Family Service and Travelers Aid, Inc.
Newport News, Va.

Mental Health Center of Norfolk and Chesapeake
Norfolk, Va.

Richmond City District Health Department
Richmond, Va.

Roanoke City Health Department
Roanoke, Va.

Bureau of Rehabilitation of the National Capital Area
Washington, D.C.

Community Addiction Treatment Center
Narcotic Treatment Agency
Washington, D.C.

Charleston Guidance Clinic
Charleston, W.Va.

DHEW Region IV

Hill Crest Hospital
Birmingham, Ala.

Henderson Clinic
Fort Lauderdale, Fla.

Mental Health Clinic of Jacksonville, Inc.
Jacksonville, Fla.

Christian Community Service Agency
Miami, Fla.

Guidance Center of Hillsboro County
Tampa, Fla.

Mental Health Association of Palm Beach County, Inc.
West Palm Beach, Fla.

Georgian Clinic Division
Georgia Mental Health Institute
Atlanta, Ga.

Peachtree-Park Wood Hospital, Inc.
Atlanta, Ga.

Mental Health Center
Tri-County Hospital
Fort Oglethorpe, Ga.

Floyd County Health Department
Rome, Ga.

University of Kentucky Research Foundation
University of Kentucky Medical Center
Lexington, Ky.

Lousiville Region 8 Mental Health and Mental Retardation Board
Louisville, Ky.

Green River Comprehensive Care Center
Owensboro, Ky.

Mr. James F. Lee
Ackerman, Miss.

North Carolina Division of Vocational Rehabilitation
Asheville, N.C.

North Carolina Division of Vocational Rehabilitation
Charlotte, N.C.

North Carolina Division of Vocational Rehabilitation
Duke University Hospital
Durham, N.C.

North Carolina Division of Vocational Rehabilitation
Durham, N.C.

North Carolina Division of Vocational Rehabilitation
Hickory, N.C.

Greenville Area Mental Health Center
Greenville, S.C.

Beckman Center for Mental Health Services
Greenwood, S.C.

Columbia Area Mental Health Center
Columbia, S.C.

Helen Ross McNabb Center
University of Tennessee Hospital Complex
Knoxville, Tenn.

Alcoholism Clinic
Tennessee Psychiatric Hospital and Institute
Memphis, Tenn.

Dr. Francis H. Deter
Murfreesboro, Tenn.

DHEW Region V

Southwest Indiana Adult Mental Health Clinic
Evansville, Ind.

Mental Health Services
Adult Psychiatric Center of N.E. Indiana
Fort Wayne, Ind.

North Side Psychiatric Center
Indianapolis, Ind.

Behavior Research and Action in the Social Sciences Foundation
Chicago, Ill.

Erie Neighborhood House
United Christian Community Service
Chicago, Ill.

Near North Family Guidance
Chicago, Ill.

St. Leonard's House
Chicago, Ill.

Family Services Association of Oak Park and River Forest
Oak Park, Ill.

Oakland County Community Mental Health Service Board
Birmingham, Mich.

Wayne County Alcoholism and Drug Abuse Service
Detroit, Mich.

Mott Vocational Guidance Center
Flint, Mich.

Ingham County Mental Health Board
Lansing, Mich.

Child and Family Service of Saginaw
Saginaw, Mich.

Catholic Welfare Service of Minneapolis
Minneapolis, Minn.

Catholic Social Service of St. Paul
St. Paul, Minn.

Division of Vocational Rehabilitation
St. Paul, Minn.

Ohio Valley Goodwill Industries Rehabilitation Center
Cincinnati, Ohio

Talbert Halfway House
Cincinnati, Ohio

Vocational Guidance and Rehabilitation Service
Cleveland, Ohio

Alvis House
Columbus, Ohio

Columbus Area Community Mental Health Center
Columbus, Ohio

Correctional Association
Dayton, Ohio

Child and Family Service
Toledo, Ohio

Wisconsin Correctional Service
Milwaukee, Wis.

DHEW Region VI

Family Service-Travelers Aid Agency
Ft. Smith, Ark.

Family Service Agency of Pulaski County
Little Rock, Ark.

Family Counseling Service of East Baton Rouge Parish, Inc.
Baton Rouge, La.

Tulane University School of Medicine
Department of Psychiatry and Neurology
New Orleans, La.

Bernalillo County Mental Health Mental Retardation Center
Albuquerque, N.Mex.

Sunbeam Home and Family Service
Oklahoma City, Okla.

Dr. James O'Carroll
Tulsa, Okla.

Family and Children Services, Inc.
Tulsa, Okla.

Tulsa Psychiatric Foundation, Inc.
Tulsa, Okla.

Amarillo Mental Health-Mental Retardation
Amarillo, Tex.

Austin-Travis County Mental Health and Mental Retardation Center
Austin, Tex.

Family and Children's Service
Beaumont, Tex.

Family Service Agency
Corpus Christi, Tex.

Dallas Rehabilitation Institute
Dallas, Tex.

Family Service of El Paso
El Paso, Tex.

Family Service Association of Fort Worth
Fort Worth, Tex.

Rio Grande State Center
Mental Health and Mental Retardation
Harlingen, Tex.

Vocational Guidance Service
Houston, Tex.

South Plains Guidance Center
Lubbock, Tex.

Family Guidance and Consultation Service
Marshall, Tex.

The Patrician Movement
San Antonio, Tex.

Mental Health and Mental Retardation Center
Waco, Tex.

DHEW Region VII

Central Kansas Mental Health Center
Salina, Kans.

Greater Kansas City Mental Health Foundation
Kansas City, Mo.

Malcolm Bliss Mental Health Center
St. Louis, Mo.

Family and Child Service
Omaha, Nebr.

DHEW Region VIII

Denver Department of Health and Hospitals
Denver, Colo.

Larimer County Mental Health Clinic
Fort Collins, Colo.

Southern Colorado Comprehensive Mental Health Center
Colorado State Hospital
Pueblo, Colo.

University of Utah
Alcoholism Clinic
Salt Lake City, Utah

DHEW Region IX

Mohave Mental Health Clinic
Kingman, Ariz.

St. Joseph's Hospital and Medical Center
Phoenix, Ariz.

Family Counseling Agency
Tuscon, Ariz.

Carmel Institute for Transactional Analysis
Carmel, Calif.

Family Service Center
Fresno, Calif.

Family Service of Long Beach
Long Beach, Calif.

Narcotics Prevention Project
Boyle Heights Center
Los Angeles, Calif.

Merced County Mental Health Service
Merced, Calif.

Catholic Social Service
Oakland, Calif.

Family Services Association of Riverside
Riverside, Calif.

Sacramento County Mental Health Services
Sacramento, Calif.

Catholic Family Service
San Diego, Calif.

Westside Community Mental Health Center, Inc.
San Francisco, Calif.

Santa Clara County Health Department
San Jose, Calif.

Family Service Agency
Santa Barbara, Calif.

Child and Family Service
Honolulu, Hawaii

Family Counseling Service of Clark County
Las Vegas, Nev.

DHEW Region X

Langdon Psychiatric Clinic
Anchorage, Alaska

Alcohol and Drug Section
Mental Health Division
Board of Control
Portland, Oreg.

Community Psychiatric Clinic, Inc.
Seattle, Wash.

Spokane Mental Health Coordinating Association
Spokane, Wash.

Narcotic Center of Tacoma-Pierce County
Tacoma, Wash.

Yakima County Mental Health Facility
Yakima, Wash.

Family Therapy

Family therapy has emerged as one of the most remarkable developments in psychiatry and the nonmedical mental health professions over the past decade. A report entitled *The Field of Family Therapy,* recently released by the Group for the Advancement of Psychiatry, provides an overview of this field, examining many of the technical, conceptual, and ethical aspects of the discipline.

Each chapter deals with a specific issue in family therapy, discussing its many ramifications and illustrating, by means of responses drawn from questionnaires distributed to a number of family therapists, how therapists treat these problems in their own practices. Special attention is given to the variety of possible ways of viewing family therapy. For example, families can be viewed as complicating factors in an individual member's emotional development or as dynamic forces that determine the responses and attitudes of its members. These different conceptual approaches give rise to differences in treating the families. Differences in theoretical approach and in treatment orientation result in different primary and secondary goals in therapy.

Copies of *The Field of Family Therapy,* GAP Publication No. 78, may be obtained at $3.00 each from the Publications Office, Group for the Advancement of Psychiatry, 419 Park Avenue South, New York, N.Y. 10016.

* U.S. GOVERNMENT PRINTING OFFICE: 1970—O 435–719/2

recent nimh publications

Single copies of these publications may be obtained from the Office of Communications, National Institute of Mental Health, LL02, 5454 Wisconsin Ave., Chevy Chase, Maryland 20015. A complete list of all publications available from the NIMH may also be obtained from the Office of Communications. If a price is given, the publication may be ordered in quantity from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402. Enclose a check or money order payable to the Superintendent of Documents.

The Family in the Hospital. This is a 313-page, illustrated report on the part played by families in patient care in hospitals abroad—especially in Africa, the Middle East, India, and Southeast Asia. By John E. Bell. Public Health Service Publication No. 1933. $1.50.

The Role of Federal Agencies in the Crime and Delinquency Field. This listing of various Federal assistance programs was compiled to assist State and local officials and administrators of public and private agencies. Information of two kinds is included: descriptions of Federal programs under which projects in delinquency and crime have been, or legally could be, funded or receive technical assistance; and examples of projects funded or assisted under particular programs. Prepared by the Center for Studies of Crime and Delinquency, NIMH National Clearinghouse for Mental Health Information Publication No. 5029. $1.25.

Comprehensive Community Services for Alcoholics. This publication is made up of the papers presented at the Workshop on Comprehensive Community Services for Problem Drinkers and Their Families held in Williamsburg, Va., in February 1969 and sponsored by the National Center for the Prevention and Control of Alcoholism. Public Health Service Publication No. 2060. 65¢

Bibliography on Epidemiology of Mental Disorders, 1966–1968. This bibliography contains 1,428 citations categorized under the topics of design and implementation of studies, etiology of mental disease, rates of disease, characteristics of populations, services and programs, and outcome of treatment. An author index and a subject index are included. Prepared by Jack Zusman, M.D., M.P.H., Virginia Hannon, M.S.W., Sc.D., Ben Z. Locke, M.S., and Miriam Geller, B.A. National Clearinghouse for Mental Health Publication No. 5030. $1.25.

Occupational Mental Health Notes, April 1970 and June 1970. OMH Notes is issued at irregular intervals and is directed to the scientific and professional community interested in occupational mental health and to executives in management and labor.

NDH DEC RMP
MAYO CLINIC LIBRARY
200 FIRST ST S W
ROCHESTER MN 55901

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
HEALTH SERVICES AND MENTAL HEALTH ADMINISTRATION
NATIONAL INSTITUTE OF MENTAL HEALTH
5454 WISCONSIN AVENUE
CHEVY CHASE, MARYLAND 20015

OFFICIAL BUSINESS

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF H.E.W.